BJS

British Journal of SURGERY

Volume 87
Number 6
June 2000

42

IN THIS ISSUE

- Fournier's gangrene: a review of 1726 cases
- Risk factors for postoperative death following elective surgical repair of abdominal aortic aneurysm: results from the UK Small Aneurysm Trial
- Randomized clinical trial of the effect of needle gauge and local anaesthetic on the pain of breast fine-needle aspiration cytology
- Long-term results of a randomized clinical trial between laparoscopic hernioplasty and Shouldice repair

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ISSN 0007-1323

ABBREVIATED PRESCRIBING INFORMATION

Indications: Tazocin is a broad spectrum bactericidal penicillin for the treatment of the following infections caused by sensitive bacteria - lower respiratory tract infections, urinary tract infections, intra-abdominal infections, skin infections, septicaemia and polymicrobic intra-abdominal, skin and lower respiratory tract infections, patients with impaired host defences and in combination with an aminoglycoside in adult and paediatric patients with neutropenia. Dosage (intravenous use only): Adults/elderly/children over 12: Usually 4.5g every 8 hours (range from 2.25-4.5g every 6-8 hours dependent on the severity). In neutropenia 4.5g every 6 hours in combination with an aminoglycoside. Children 12 years and under: Only recommended for children with neutropenia. Dosage as for adults with neutropenia unless weighing < 50kg when 90mg/kg every 6 hours, in combination with an aminoglycoside, is recommended. Renal Impairment: Dosing reduction may be necessary, please consult data sheet. Contra-indications: Hypersensitivity to penicillin, cephalosporin or β-lactamase inhibitors. Warnings: Discontinue if anaphylactic or allergic reaction occurs. Precautions: Periodic assessment of renal, hepatic and haematological function advised. Discontinue if bleeding manifestations occur. Resistant bacteria may cause superinfection. Convulsions may occur with higher than recommended doses. Possibility of hypokalaemia in patients with low potassium or on cytotoxics or diuretics. Evaluate patients for syphilis prior to treatment for gonorrhoea. Use during pregnancy or lactation: Only if benefit outweighs risk. Side-effects: Most frequent: gastro-intestinal disturbances; various skin reactions including rashes, erythema, pruritus and urticaria, allergic reactions, superinfection, phlebitis, thrombophlebitis, pain/inflammation at site of injection. Less frequent: muscle pain or weakness, hallucination, dry mouth, stomatitis, sweating, oedema, tiredness and rarely leucopenia, interstitial nephritis. Haematological changes, increases in liver and rarely renal function test values have been reported. Overdose: Piperacillin may be reduced by dialysis. Presentation: Tazocin 2.25g: Vials containing piperacillin 2g (as piperacillin sodium) and tazobactam 250mg (as tazobactam sodium). Tazocin 4.5g: Vials containing piperacillin 4g (as piperacillin sodium) and tazobactam 500mg (as tazobactam sodium). Basic NHS Price: 4.5g strength - single vial £13.16, single infusion pack £14.48; 2.25g strength single vial £7.24. PL nos: 4.5g strength PL 0095/0254, 2.25g strength PL 0095/0252. PA nos: 4.5g vials 37/68/2, 4.5g combipack 37/68/3, 2.25g vial 37/68/1. Legal Category: POM. Further information is available on request from: Wyeth Laboratories, Huntercombe Lane South, Taplow, Maidenhead, Berks. SL6 0PH. Tel (01628) 604377. Product Licence Holder: Cyanamid of Great Britain Limited, Cyanamid House, Fareham Road, Gosport, Hampshire. PO13 0AS.
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P. 25,313

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48

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The *British Journal of Surgery* ISSN 0007-1323

Published on behalf of the British Journal of Surgery Society. All queries regarding submitted papers not yet accepted for publication should be addressed to:
Joint Editors, *British Journal of Surgery*, Blackwell Science Ltd,
25 John Street, London WC1N 2BL, UK (Tel: +44 171 404 1831).

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The Publisher's policy is to use acid-free permanent paper, to the draft standard ISO/DIS/9706, made from sustainable forests using chlorine-free pulp. The paper used in this journal has an ECO-CHECK 4-star rating.

The *British Journal of Surgery* has a worldwide website at: http://www.bjs.co.uk

A microfilm version of the *British Journal of Surgery* is available. Please contact University Microfilms Inc, 300 N. Zeeb Road, Ann Arbor, Michigan 48106, USA.

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Typeset and printed by Information Press Ltd, Oxford

*Periodicals postage is paid at Rahway, NJ and Additional Mailing offices. Postmaster: send address corrections to: the *British Journal of Surgery*, c/o Mercury Airfreight International Ltd, 365 Blair Road, Avenel, NJ 07001, USA.

Contents

British Journal of Surgery

Volume 87, Issue 6, June 2000

Leading article

689 **Slowing the heart saves lives: advantages of perioperative β-blockade**
K. G. Jones and J. T. Powell

Surgical publishing

691 **Writing the manuscript**
S. A. Wells Jr.

693 **COPE – Guidelines on good publication practice**

Clinical dilemma

694 **Problematic diagnosis of a breast lesion**
K. Sandelin

Reviews

695 **The evolution of nutritional support in acute pancreatitis**
D. N. Lobo, M. A. Memon, S. P. Allison and B. J. Rowlands
Larger trials are still needed

708 **Hereditary pancreatitis and mutations of the cationic trypsinogen gene**
D. A. O'Reilly and A. N. Kingsnorth
Possibly should be screened for in all patients with acute pancreatitis

718 **Fournier's gangrene: a review of 1726 cases**
N. Eke
Diagnosis is made on clinical grounds but controversy remains over definition

Digest

729 ***Surgery Today***
S. Matsuno

Vascular Surgical Society

734 **Reperfusion injury is greater with delayed restoration of venous outflow in experimental concurrent arterial and venous limb injury**
D. W. Harkin, A. A. B. Barros D'Sa, M. M. I. Yassin, I. S. Young, J. McEneny, D. McMaster, M. D. McCaigue, M. I. Halliday and T. G. Parks
Experimental justification for the use of temporary intraluminal stunts in complex limb trauma

742 **Risk factors for postoperative death following elective surgical repair of abdominal aortic aneurysm: results from the UK Small Aneurysm Trial**
A. R. Brady, F. G. R. Fowkes, R. M. Greenhalgh, J. T. Powell, C. V. Ruckley, and S. G. Thompson, on behalf of the UK Small Aneurysm Trial Participants
Preoperative lung and renal function were strongly associated with postoperative death

750 **Population screening reduces mortality from aortic aneurysm in men**
B. P. Heather, K. R. Poskitt, J. J. Earnshaw, M. Whyman and E. Shaw
More evidence that aneurysm screening reduces the mortality rate in men

754 **Randomized, multicentre, double-blind, placebo-controlled trial of the use of aprotinin in the repair of ruptured abdominal aortic aneurysm**
J. Robinson, S. Nawaz and J. D. Beard, on behalf of the Joint Vascular Research Group
Did not affect outcome in this trial including 77 patients

758 **Two-year results of a randomized controlled trial of rifampicin bonded extra-anatomic Dacron grafts (short note)**
J. J. Earnshaw, B. Whitman, B. P. Heather and on behalf of the Joint Vascular Research Group
Antibiotic bonding cannot prevent vascular graft infection

The Royal College of
Surgeons of Edinburgh

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Ductal Calculi: The Laparoscopic Approach

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760 **Apolipoprotein E genotype is associated with differential expansion rates of small abdominal aortic aneurysms**
L. U. Gerdes, J. S. Lindholt, S. Vammen, E. W. Henneberg and H. Fasting
A preliminary study including 57 men

766 **Clinical governance and the vascular surgeon**
C. D. Irvine, D. Grayson and R. J. Lusby
Comparison of crude mortality rates is not enough

771 **Use of superficial femoropopliteal vein for suprainguinal arterial reconstruction in the presence of infection**
C. P. Gibbons, C. J. Ferguson, K. Edwards, D. E. Roberts and H. Osman
Encouraging results for a technically challenging procedure

Randomized clinical trials

777 **Randomized clinical trial of the effect of needle gauge and local anaesthetic on the pain of breast fine-needle aspiration cytology**
I. R. Daltrey and M. W. Kissin
Blue-hub (23G) needle was least painful

780 **Long-term results of a randomized clinical trial between laparoscopic hernioplasty and Shouldice repair**
B. J. Leibl, P. Däubler, C.-G. Schmedt, K. Kraft and R. Bittner
Is the short-term TAPP less painful than the conventional Shouldice hernia repair

Original articles

784 **Beneficial effects of arterialization of the portal vein on extended hepatectomy**
Y. Shimizu, M. Miyazaki, H. Shimizu, H. Ito, K. Nakagawa, S. Ambiru, H. Yoshidome and N. Nakajima
Arterialization of the portal vein improves survival after experimental extended hepatectomy

790 **Experimental study of a novel fibrin sealant for achieving haemostasis following partial hepatectomy**
B. R. Davidson, S. Burnett, M. S. Javed, A. Seifalian, D. Moore and N. Doctor
Reduced bleeding and the time to haemostatis of the liver surface

796 **Duplex-guided thrombin injection for iatrogenic femoral artery pseudoaneurysm is effective even in anticoagulated patients**
A. F. Lennox, K. T. Delis, G. Szendro, M. B. Griffin, A. N. Nicolaides and N. J. Cheshire
Effective in all 30 patients treated

802 **Functional outcome after restorative panproctocolectomy for ulcerative colitis decreases an otherwise enhanced quality of life**
A. O'Bichere, K. Wilkinson, S. Rumbles, C. Norton, C. Green and R. K. S. Phillips
Poor function after pelvic pouch surgery offsets any quality of life advantage in body image over ileostomy

808 **Immunoglobulin G and albumin levels in whole gut lavage fluid provide an objective measure of pouch ileitis**
N. Evgenikos, D. C. C. Bartolo, D. W. Hamer-Hodges and S. Ghosh
May be useful in measuring disease activity

814 **On-line quantitative analysis of surface electromyography of the pelvic floor in patients with faecal incontinence**
A. S. Gee, R. S. J. Jones and P. Durdey
May replace invasive EMG

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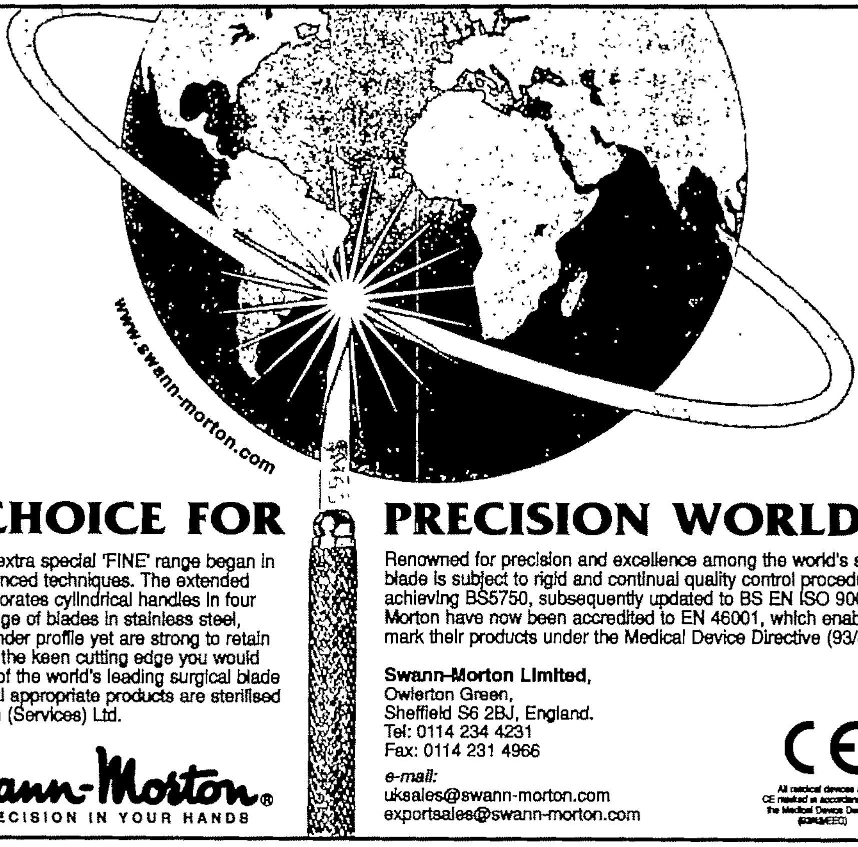

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819 **Long-term results of arteriovenous fistulas using transposed autologous basilic vein**
G. J. Murphy, S. A. White, A. J. Knight, T. Doughman and M. L. Nicholson
May be better than a PTFE interposition graft

824 **Value of herniography in the management of occult hernias and chronic groin pain in adults (short note)**
F. Calder, R. Evans, D. Neilson and P. Hurley
A valuable test in patients with intractable groin pain

826 **Correspondence**

829 **Book reviews**

830 **Scientific surgery**

831 **Instructions to authors**

0007-1323(200006)87:6;1-V

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Colin Mumford

June 2000, 56 pages, 6 illustrations, 0-632-05527-8, £8.50

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Table of Contents: ***1) Introduction***; What the book is for; Why interview success is vital; Good interview technique can be learned
2) Before the Interview; Spotting the advert; The "Commando Operation" to get on the shortlist; To visit or not to visit; Who to see once you are shortlisted; Getting the CV right; How to choose a winning referee (or three)
3) The Interview; Where, when and how; What to wear; How to smell; How to sit; Eye contact, where to look and the CV run-through; Gesture; How to end the interview
4) The Questions; Inevitable questions; Probable questions; Problem questions and how to escape; "Cringe" questions; Googlies; Handling the "Vicar's Wife"; Fell walking and motorbikes; "Any questions for the panel...?"
5) After the Interview; The job offer; Negotiation, how, where and who with?; Salary; Office and secretary; What if you weren't successful?
6) Conclusion; Summary; Check-lists; Disclaimer

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Contents

British Journal of Surgery

Volume 87, Issue 7, July 2000

Leading article

833 **The effect of litigation on surgical practice in the USA**
J. E. Fischer
The first of three articles on medicolegal activity

Surgical publishing

835 **The 'foreign' author**
M. Rothmund and A. Fingerhut

837 **COPE – Guidelines on good publication practice**

Clinical dilemma

838 **A problem bile duct stone**
R. Van Hee

Reviews

840 **Molecular technology and pancreatic cancer**
M. Manu, J. Buckels and S. Bramhall
Pancreatic cancer is the 5th leading cause of cancer death in the Western World

854 **Mesh compared with non-mesh methods of open groin hernia repair: systematic review of randomized controlled trials**
EU Hernia Trialists Collaboration
Mesh repairs associated with fewer recurrences

860 **Laparoscopic compared with open methods of groin hernia repair: systematic review of randomized controlled trials**
EU Hernia Trialists Collaboration
The jury is still out

Randomized clinical trials

868 **Randomized clinical trial of micronized flavonoids in the early control of bleeding from acute internal haemorrhoids**
M. C. Misra and R. Parshad
MPFF may assist in deferring definitive therapy to a more convenient time

873 **Randomized clinical trial of laparoscopic *versus* open fundoplication: blind evaluation of recovery and discharge period**
G. Nilsson, S. Larsson and F. Johnsson
Laparoscopic technique takes longer but hospital stay shorter

Original articles

879 **Preoperative portal vein embolization improves prognosis after right hepatectomy for hepatocellular carcinoma in patients with impaired hepatic function**
H. Tanaka, K. Hirohashi, S. Kubo, T. Shuto, I. Higaki and H. Kinoshita
Improves survival in patients with impaired hepatic function

883 **Pancreatic fistula after pancreatic head resection**
M. W. Büchler, H. Friess, M. Wagner, C. Kulli, V. Wagener and K. Z'graggen
Uncommon and easily managed non-operatively

890 **Changing referral pattern of biliary injuries sustained during laparoscopic cholecystectomy (Short note)**
S. R. Shah, D. F. Mirza, R. Afonso, A. D. Mayer, P. McMaster and J. A. C. Buckels
More patients are being referred earlier

892 **Prognosis and surgical management of patients with palpable inguinal lymph node metastases from melanoma**
T. M. D. Hughes, R. P. A'Hern and J. M. Thomas
Combined lymph node dissection impaires local control but not survival

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[illegible]

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902 **Experimental study of faecal continence and colostomy irrigation**
A. O'Bichere, P. Sibbons, C. Doré C. Green and R. K. S. Phillips
Antegrade irrigation via a Malone conduit may be indicated in certain patients

909 **Morbidity and functional outcome after double dynamic graciloplasty for anorectal reconstruction**
E. Rullier, F. Zerbib, C. Laurent, M. Caudry and J. Saric
Single dynamic graciloplasty preferable to the double version

914 **In-hospital delay in the diagnosis of breast cancer**
D. C. Jenner, A. Middleton, W. M. Webb, R. Oommen and T. Bates
It is suggested that fewer than 40% women should have the diagnosis delayed over 12 weeks

920 **Clinical relevance of sentinel lymph nodes outside the axilla in patients with breast cancer**
L. Jansen, M. H. E. Doting, E. J. Th. Rutgers, J. de Vries, R. A. Valdés Olmos and O. E. Nieweg
Present in 19% patients, but detection seldom changed management

926 **Transvenous sclerotherapy for huge oesophagogastric varices using open injection sclerotherapy**
S. Kitano, D. Baatar, T. Bandoh, T. Yoshida, S. Tsuboi and T. Matsumoto
A novel approach to sclerotherapy for oesophygeal varices

931 **Surgical Infection Society of Europe Abstracts**

965 **Correspondence**

971 **Book reviews**

974 **Scientific surgery**

975 **Instructions to authors**

0007-1323(200007)87:7;1-R

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Contents

British Journal of Surgery

Volume 87, Issue 8, August 2000

Leading article

977 **Litigation and surgical practice in the UK**
H. Goodwin

Surgical publishing

980 **The final product**
J. A. Murie

Clinical dilemma

983 **Soft tissue sarcoma involving the sciatic nerve**
M. F. Brennan

Reviews

984 **Portal flow augmentation for liver cirrhosis**
L. R. Jiao, A. M. Seifalian, R. T. Mathie, N. Habib and B. R. Davidson
May be useful but more evaluation is needed

992 **E-cadherin-catenin cell-cell adhesion complex and human cancer**
B. P. L. Wijnhoven, W. N. M. Dinjens and M. Pignatelli
Not just a 'sticky molecular complex'

1006 **Hyperthermic intraperitoneal chemoperfusion in the treatment of locally advanced intra-abdominal cancer**
W. P. Ceelen, U. Hesse, B. de Hemptinne and P. Pattyn
A growing body of evidence supports this technique, phase III trials are awaited

Digest

1016 **Annales de Chirurgie**
D. Castaing

Original articles

1019 **The severity of acute pancreatitis: a multivariate analysis of oxidative stress markers and modified Glasgow criteria**
F. M. Abu-Zidan, M. J. D. Bonham and J. A. Windsor
Oxidative stress markers correlate with severity of acute pancreatitis but may not have greater predictive value than Glasgow

1024 ***In vivo* evaluation of an implantable portal pump system for augmenting liver perfusion**
L. R. Jiao, A. M. Seifalian, B. R. Davidson and N. Habib
An experimental study that shows development of the pump may benefit patients with cirrhosis

1030 **Analysis of 153 gunshot wounds of the liver**
J. D. F. Marr, J. E. J. Krige and J. Terblanche
Most liver gunshot injuries can be managed with simple surgical techniques

1035 **Expression and processing of gastrin in pancreatic adenocarcinoma**
M. Caplin, K. Savage, K. Khan, B. Bret, J. Rode, A. Varro and A. Dhillon
Pancreatic cancer cells express gastrin receptors, may lead to new treatment options

1041 **Diagnosis and management of cystic pancreatic tumours with mucin production**
Y. Shima, M. Mori, N. Takakura, T. Kimura, T. Yagi and N. Tanaka
A management strategy is proposed

1048 **Influence of a specialised leg ulcer service on management and outcome**
A. S. K. Ghauri, M. C. Taylor, J. E. Deacon, M. R. Whyman, J. J. Earnshaw, B. P. Heather and K. R. Poskitt
Enthusiasts get better reslts

1057 **Effect of contralateral disease on duplex measurements of internal carotid artery stenosis**
S. A. Ray, S. J. M. Lockhart, R. Dourado, A. T. Irvine and K. G. Burnand
Contralateral carotid stenosis may be overestimated by duplex

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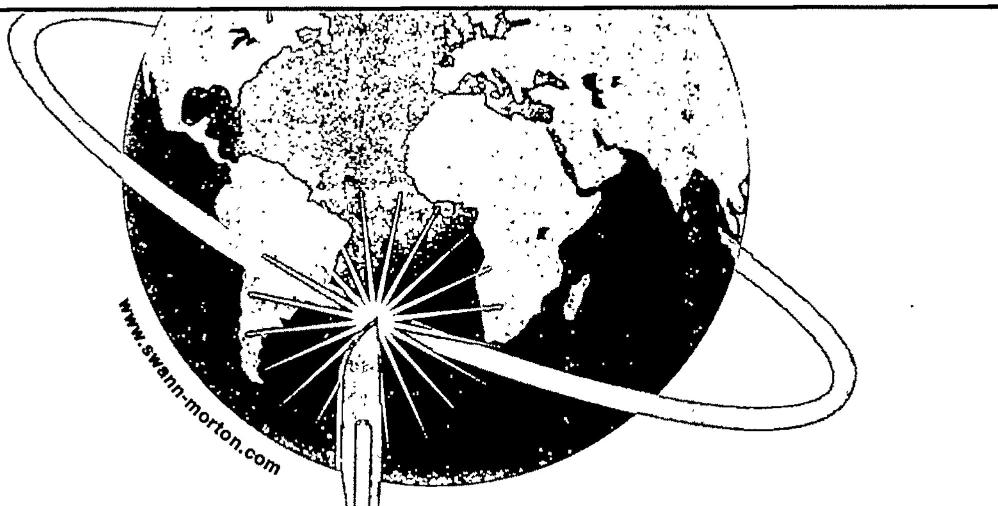

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1063 **The role of a defunctioning stoma in the management of large bowel Crohn's disease**
C. M. Edwards, B. D. George, D. P. Jewell, B. F. Warren, N. J. McC. Mortensen and M. G. W. Kettlewell
Clinical remission induced by diversion may not last

1067 **Bascom's operation in the day-surgical management of symptomatic pilonidal sinus**
A. Senapati, N. P. J. Cripps and M. R. Thompson
Simple day case technique

1071 **Compression anastomoses (AKA-2) in colorectal surgery: results in 442 consecutive patients**
C. Wullstein and E. Gross
Compression anastomosis is safe in colorectal surgery

1076 **Analysis of risk factors for nosocomial sepsis in surgical patients**
C. Fariñas-Álvarez, M. C. Fariñas, C. Fernández-Mazarrasa, J. Llorca, D. Casanova and M. Delgado-Rodríguez
Patient related factors are more important than those related to surgery

1082 **Impact of the '2 week wait' directive for suspected cancer on service provision in a symptomatic breast clinic**
P. J. Cant and D. S. L. Yu
Do Government waiting time directives for cancer advantage patients with symptomatic breast disease?

1087 **Cholecystectomy, peptic ulcer disease and the risk of adenocarcinoma of the oesophagus and gastric cardia**
J. Freedman, J. Lagergren, R. Bergström, E. Näslund and O. Nyrén
Cholecystectomy does not increase risk

1094 **Role of xanthine oxidase in small bowel mucosal dysfunction after surgical stress**
R. Anup, P. Susama and K. A. Balasubramanian
Evidence that xanthine oxidase plays a major role

1102 **Oesophageal resection for high-grade dysplasia in Barrett's oesophagus**
G. Zaninotto, A. R. Parenti, A. Ruol, M. Costantini, S. Merigliano and E. Ancona
Rational therapy in patients fit for surgery

1106 **Comparison of preoperative risk analysis in patients with adenocarcinoma or squamous carcinoma of the oesophagus**
E. Bollschweiler, W. Schröder, A. H. Hölscher and J. R. Siewert
Different risk profiles in this study of 325 patients

1111 **Multicentre study of thyroid nodules in patients with Graves' disease**
J. L. Kraimps, M. H. Bouin-Pineau, M. Mathonnet, L. de Calan, J. Ronceray, J. Visset, R. Marechaud and J. Barbier
An argument in favour of surgery because of the incidence of carcinoma

1114 **Correspondence**
1116 **Book reviews**
1118 **Scientific surgery**
1119 **Instructions to authors**

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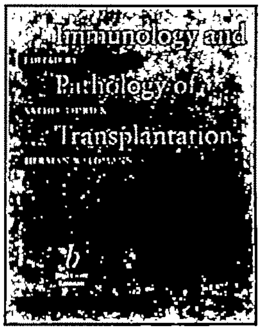
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Leading article

Slowing the heart saves lives: advantages of perioperative β-blockade

K. G. Jones and J. T. Powell

Department of Vascular Surgery, Charing Cross Hospital, London W6 8RF, UK

The average age of patients undergoing major surgery continues to rise, and attempts to stratify risk and improve surgical outcome have led to an ever-expanding range of costly preoperative investigations. This is particularly evident in vascular surgery where the perioperative cardiovascular event rate is about 8 per cent[1]. While we may be identifying risk, are we ignoring simple measures that may improve outcome? Two such measures have emerged recently: first, the use of perioperative β-blockade and, second, the administration of a (validated) revised Goldmann Cardiac Risk Index based on clinical judgement aided by routine investigations.

The first large trial showing the benefits of perioperative β-blockade was reported 4 years ago[2]. Two hundred patients, considered at high risk of cardiac complications and undergoing major abdominal or vascular surgery, were randomized into two equal groups to receive perioperative treatment with either atenolol or placebo. The death rate from both cardiac and all causes was significantly lower in the atenolol group throughout the postoperative period. After 8 months there were seven cardiac deaths in the placebo group and none in the atenolol group ($P < 0{\cdot}001$). Even after 2 years only 4 per cent had died from cardiac causes in the atenolol group compared with 12 per cent in the placebo group ($P = 0{\cdot}033$).

Last year a trial of perioperative bisoprolol in patients at extremely high risk of cardiac complications while undergoing vascular surgery was stopped early after interim analysis[3]. The 112 patients had been selected from a cohort of 1351 by dobutamine echocardiography. Active treatment with bisoprolol reduced their risk of a cardiovascular event in the first 30 days after surgery from 34 per cent in the normal care group to just 3 per cent. Although this was a highly selected group, one might wonder if the results could be generalized. In several smaller trials, involving procedures ranging from endoscopic retrograde cholangiography to carotid endarterectomy, β-blockade has been shown to reduce peak heart rate (at intubation and extubation) and perioperative ischaemia. The reduction in perioperative ischaemia is likely to arise through several synergistic mechanisms. The reduction in heart rate and myocardial contractility, together with redistribution of blood flow from normal regions to ischaemic zones, improves myocardial oxygen balance. β-blockade also suppresses lipolysis and causes the myocardium to metabolize glucose in preference to fatty acids, a measure likely to diminish myocardial oxygen consumption. The improved myocardial oxygen balance in the vulnerable period, the first 3 days after surgery, is likely to be the central mechanism underlying the findings (in favour of β-blockade) of the two recent large trials outlined above[2,3].

β-blockers are cheap and safe. They could be used in much simpler perioperative regimens than those described in the recent trials. What is the argument against using them for all surgery in older patients? Certainly there is a minority of patients who are intolerant of β-blockers or who have reactive airways disease, but they can be identified following a test dose of a cardioselective β-blocker. Evidence from well conducted clinical trials to support the routine use of β-blockers in all older patients undergoing abdominal surgery, and in all patients undergoing vascular surgery, is not yet available. Nevertheless, should we really hold back while such evidence is collected?

Nearly all patients undergoing vascular surgery have concomitant coronary artery disease, often with silent myocardial ischaemia. For those undergoing major abdominal surgery there is a simple method of evaluating cardiac risk, with minimum resource implications – a revised Goldmann Cardiac Risk Index[4]. Last year Lee *et al.*[4] assessed risk factors in a cohort of 2893 patients undergoing major surgery, derived a simple index and validated it prospectively in a further 1422 patients. Patients with fewer than two of the following factors were at very low risk of postoperative cardiac complications: high-risk abdominal surgery, known history of ischaemic heart disease, congestive heart failure (on examination, history or chest radiograph), previous stroke or transient ischaemic attack, insulin-dependent diabetes, creatinine level above 177 μmol/l. Patients with two or more of these risk factors had a 6 per cent risk of cardiac complications[4].

In summary, there are two simple measures that could be used in combination to improve the outcome of major surgical procedures, with minimum resource implications. First, apply the revised Goldmann Cardiac Risk Index[4]. Second, use perioperative β-blockade for those with two or more simple cardiac risk factors. For vascular surgical patients, where the risk of cardiac complications is high, perhaps a single simple measure is sufficient to improve outcome: perioperative β-blockade. The authors are testing this in a clinical trial.

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Writing the manuscript

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Writing well is difficult, particularly when it comes to scientific topics, since the subject is complex and often of interest only to a limited audience. However, there are many examples of good scientific writing, the skill being to convey one's message simply so that it is easily understood and absorbed by the reader. A published body of work, whether performed in the laboratory or the clinic, should be looked on as an academic currency. Aspiring basic or clinical scientists feel an enormous pressure to establish themselves as accomplished clinical or laboratory investigators, realizing that academic promotion, election to membership of distinguished societies, and consideration for senior leadership positions at prestigious institutions are largely determined by an evaluation of a candidate's publications. Often young scientists place undue emphasis on the number of scientific publications, rather than the quality. However, discerning promotion, selection or search committees, charged with judging a candidate's worth, rarely confuse quantity and quality. Therefore, much thought should be given to what to write and where to publish the work, as a permanent record is being established that will represent one's academic accomplishments.

Types of manuscript

Surgical articles are usually written in one of three forms: case reports of a clinical observation, scientific reviews and original scientific articles based on either laboratory or clinical research. Whatever the form, one should strive for clarity, remembering that scientific writing is by necessity highly structured and thinly prosaic. If the study is well designed, the methodology appropriate for the experiment, and the results clear, the author's work should be relatively easy.

The case report

Some surgeons find a clinical case of great interest and decide to record it, usually in the form of a 'case report and review of the literature'. Clinical case reports are usually the work of young authors and represent an early attempt at medical publication. These articles rarely signal an important clinical advance and many medical editors do not consider them for publication. Above all, case reports should be brief and carefully illustrated to emphasize the primary and hopefully novel observation.

The article review

In these publications there is a review of a single topic. The manuscripts are usually lengthy, and analyse or summarize a body of previously published work, although some authors include data from their clinic or laboratory as part of the report. The reader finds these articles valuable when seeking a broad overview of a given topic. Well written reviews take time and necessitate a careful study of the relevant literature. The task is particularly challenging when the author attempts to clarify a controversial issue.

The original scientific publication

These articles provide the backbone for the advancement of medical knowledge and represent the first line of scientific publications. The importance of an original scientific article is directly related to the quality of the experimental data on which it is based. The more important the hypothesis being tested, the better the experimental design, and the more definitive the results of the experiment, the easier it is to write the paper.

Original scientific articles usually have a standard structure consisting of: an abstract, an introduction, materials and methods, results, and the discussion. In planning the manuscript one begins with a careful analysis of the study results, as an objective review of the data will define what conclusions can be drawn. How the author handles the discussion of the materials and methods is a function of the writer's intellect and style, but it is important not to make the common mistake of drawing conclusions beyond what is defined by the results of the experimental data.

The abstract

The abstract is a brief description of the study. More commonly, structured abstracts are being used to state: the principal objectives and scope of the investigation, the methodology used, the experimental results and the conclusions of the study. The well prepared abstract enables the readers to grasp the essence of the study, to decide whether it is relevant to their interests and to determine whether the article is worth reading. The importance of the abstract is greater in the current era of online search machines, when abstracts are so readily available and retrievable. Abstracts should give an overview of the study and not exceed 250 words. Even though the abstract is the part of the article first seen by the reader, it should be written after the rest of the manuscript is completed.

The introduction

The author provides a background for the reader by defining the problem to be addressed and discussing the pertinent literature. The author might find it necessary to describe generally one or more experimental methods used in the study. The introduction is occasionally concluded with a brief statement about the results of the study but this is controversial and some authors choose to leave the important findings to the discussion.

The materials and methods

It is important that the author describe the subjects of the study, whether humans or laboratory animals, and the clinical or laboratory methods employed. If human subjects were involved it should be stated that an institutional review board approved the study. It is frequently impractical to explain a laboratory method in detail, in which case a reference to a previously published description suffices. The statistical methods should be described and referenced.

This section of the manuscript tends to be rather dry but the information is critical to the paper and precision is essential. During editorial review of the manuscript this section is evaluated carefully to determine whether the reviewer understands the methodology sufficiently to repeat the experiment. Often, one or more methods described in this section have not been reported previously and will serve as the basis for future laboratory experiments by other investigators. It is particularly important that this section be clear and uncluttered because it provides the basis for all that follows.

Clinical studies may lend themselves only to a report of a series of patients evaluated over a long period of time. If it can be achieved, the most important design of a clinical study is the prospective randomized controlled trial. With this method one obtains study groups that are balanced with regard to known baseline factors and presumably to unknown factors as well. No other study design accomplishes this. It is dismaying to see how many clinical studies compare historical controls, or a matched set of patients as controls, or even no controls, to the study group, rather than follow the more meaningful design provided by a prospective randomized trial.

The results

This section represents the heart of the manuscript and may be very short if the preceding materials and methods section, and the succeeding discussion section, are well written. The results can often be expressed in tabular form and it is not necessary to present all of the experimental data, just that which is relevant. If there is any part of the manuscript that demands crispness and clarity it is the results section as it represents new knowledge derived from the investigation.

One must guard against redundancy in the results section, not repeat in the text data that are also presented in tables or figures, and not amplify the materials and methods section in the results section.

The discussion

The purpose here is to provide an analytical interpretation of the results and to state what principles and relationships are learned. One must be careful to interpret the results yet not repeat them. In many instances it will be important to state how the experimental data contrast and compare with the results of previously reported studies. In the final section of the discussion one should state the conclusions of the study and summarize the evidence for each of them. The discussion flows directly from the sections on materials and methods and results, and it is important that there be logic to the relationship. Do not hesitate to point out any weakness in the study. Prophylactic self-criticism pre-empts readership criticism.

Authorship

Little has been said about the listing of authors but this is an important matter as it is often the source of conflict. The authors should be listed in the order in which they most contributed to the study. In some centres it has been customary for the head of a laboratory to be listed as the last author on all papers published from the group. It is my strong view that the persons primarily involved in the research should get the credit, especially younger scientists who frequently have the original idea for the study and perform most of the work. The duty of the senior scientist is to provide an intellectual milieu for younger investigators and to create an opportunity for them to grow and gain intellectual independence. Nevertheless, there are often arguments about the sequence in which contributors are listed on manuscripts and resolution of this conflict rests with the senior scientist in the laboratory where the work was performed. Trouble can usually be avoided if decisions about listing priority of authors have been taken early in the study and certainly before writing the paper. Remember that some journals limit the number of authors.

With time and practice one can master the art of writing scientific papers. Above all, it should be remembered that substance is paramount and without significant data flowing from a well designed study the style of the article will be irrelevant.

Committee on Publication Ethics

GUIDELINES ON GOOD PUBLICATION PRACTICE

6 Redundant publication

Definition

Redundant publication occurs when two or more papers, without full cross reference, share the same hypothesis, data, discussion points, or conclusions.

Action

1 Published studies do not need to be repeated unless further confirmation is required.
2 Previous publication of an abstract during the proceedings of meetings does not preclude subsequent submission for publication, but full disclosure should be made at the time of submission.
3 Re-publication of a paper in another language is acceptable, provided that there is full and prominent disclosure of its original source at the time of submission.
4 At the time of submission, authors should disclose details of related papers, even if in a different language, and similar papers, in press.

7 Plagiarism

Definition

Plagiarism ranges from the unreferenced use of others' published and unpublished ideas, including research grant applications to submission under 'new' authorship of a complete paper, sometimes in a different language.

It may occur at any stage of planning, research, writing, or publication: it applies to print and electronic versions.

Action

1 All sources should be disclosed, and if large amounts of other people's written or illustrative material is to be used, permission must be sought.

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Other sections of these guidelines will appear in future issues. The full guidelines are available at www.publicationethics.org.uk.

P, 25, 313

Clinical dilemma

Problematic diagnosis of a breast lesion

A 55-year-old woman with C4 or C5 cytology has a lesion excised. Histological examination suggests a benign pathology. How should this situation be managed? Dr Kerstin Sandelin of Stockholm replies.

First, let us consider some background. Triple assessment (clinical examination, mammography, fine-needle aspiration cytology (FNAC)) of a breast lump is an established algorithm and the combination of all three modalities increases diagnostic accuracy substantially. Ninety per cent of women with a palpable breast cancer should be diagnosed before operation, according to guidelines from the European Society of Surgical Oncology[1]. Young age, a negative history for risk factors (no breast cancer in the family, no dominant breast mass, no previous breast lumps) might justify clinical examination alone, with or without mammography or FNAC, but in postmenopausal women the risk of breast cancer increases, so triple assessment for a breast mass is unequivocally indicated[2].

Ultrasonography is a useful adjunct in experienced hands and, as a non-invasive technique, it is also helpful in combination with both mammography and FNAC for guidance. Diagnostic accuracy from FNAC can reach 95 per cent in experienced hands, especially if performed by a trained cytopathologist who reads the smears immediately. Interpretation in an indecisive situation, as in this case, is crucial. When the amount and quality of the smears are suboptimal, the cytopathological report should call for further confirmation, either by repeated FNAC, or core needle or surgical biopsy. No false-positives from FNAC occurred in one recent publication evaluating triple assessment in a symptomatic breast clinic[3]; core needle biopsy is not usually needed when FNAC is carried out and the interpretation of the smears is done by experienced aspirators. To confirm whether the tumour grows invasively or intraductally a core needle biopsy is usually necessary, although triple assessment may separate the two, especially when the assessments are implemented simultaneously.

Let us now review the present case. When considering a situation such as this, all steps must be carefully examined and questioned. First comes clinical examination to rule out that the lesion was not left behind. In a lumpy breast the wrong lesion might have been removed. Second, tissue specimen radiography is a modality that allows comparison of preoperative and intraoperative findings. Its usefulness for impalpable lesions is unquestionable but, for palpable lesions, it also adds to diagnostic accuracy if the initial lesion was mammographically apparent. There is also a good correlation between mammographic and cytological findings[3]. Third, regarding the cytological diagnosis classed as C4 or C5 (which implies a strong suspicion of malignancy), the smears should be re-read, especially by other cytopathologists, to confirm or refute the initial cancer diagnosis. At this stage possible differential diagnoses should be considered.

This review of morphology should include an examination of all slides plus additional serial sections of the whole specimen. In such circumstances tissue specimen mammography may be helpful in identifying the lesion. Finally it must be appreciated that overstaging atypical smears, compromising quantity and quality of smears, and lack of experience may attribute to a false-positive initial report. There are a number of benign conditions that should be considered at histopathological assessment, such as papillary lesions, atypical epithelial hyperplasia and fibroadenoma with extensive epithelial atypia. Smears from syringocystadenoma papilliferum may mimic breast cancer closely.

In circumstances such as those outlined initially, the patient will be confused by the uncertainty of her physician. Total openness is advised. Should the initial strong suspicion of cancer prove erroneous, it may take some time for the patient to come to terms with this fact. One final thought: there is now a substantial consensus that breast units, in which diagnosticians and therapists are integrated, provide optimal management. Such units should, therefore, have the potential of reducing the incidence of situations such as this.

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Review

Evolution of nutritional support in acute pancreatitis

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Background: Acute pancreatitis is a catabolic illness and patients with the severe form have high metabolic and nutrient demands. Artificial nutritional support should therefore be a logical component of treatment. This review examines the evidence in favour of initiating nutritional support in these patients and the effects of such support on the course of the disease.

Methods: Medline and Science Citation Index searches were performed to locate English language publications on nutritional support in acute pancreatitis in the 25 years preceding December 1999. Manual cross-referencing was also carried out. Letters, editorials, older review articles and most case reports were excluded.

Results and conclusion: There is no evidence that nutritional support in acute pancreatitis affects the underlying disease process, but it may prevent the associated undernutrition and starvation, supporting the patient while the disease continues and until normal and sufficient eating can be resumed. The safety and feasibility of enteral nutrition in acute pancreatitis have been established; enteral nutrition may even be superior to parenteral nutrition. Some patients, however, cannot tolerate enteral feeding and this route may not be practical in others. Parenteral nutrition still has a role, either on its own or in combination with the oral and enteral routes, depending on the stage of the illness and the clinical situation.

Paper accepted 7 February 2000

British Journal of Surgery 2000, 87, 695–707

Introduction

Acute pancreatitis, a disease of varying severity, has been defined as an acute inflammatory process of the pancreas, with variable involvement of other regional tissues or remote organ systems[1]. Mild disease is associated with minimal organ dysfunction and an uneventful recovery, while severe disease is associated with organ failure and local complications such as necrosis, abscess and pseudocyst formation[1]. Mild attacks account for 70–80 per cent of hospital admissions for this condition and usually resolve in 5–7 days[2–5]. The 20–30 per cent of patients with severe disease pose a clinical challenge in critical care, requiring a multidisciplinary approach that includes artificial nutritional support.

Studies on the use of nutritional support are conflicting and, in recent years, the pendulum has swung from favouring parenteral nutrition to highlighting the feasibility and safety of enteral nutrition whenever possible[6]. Guidelines published by the American College of Gastroenterology[7] recommend that parenteral nutrition should be used for patients with severe disease who will be without oral nutrition for 7–10 days. It is interesting, however, that there is no mention of nutritional support in the recent UK guidelines[8] for the management of acute pancreatitis.

This review examines the indications for artificial nutritional support, identifies which patients may require it, evaluates the available evidence on the relative merits of the enteral and parenteral routes, and assesses the potential role of novel nutritional substrates.

Search strategy

An internet-based search of the Medline and Science Citation Index databases was undertaken using the key words acute, chronic, pancreatitis, nutrition, nutritional support, enteral and parenteral in various combinations with the Boolean operators AND, OR and NOT. Emphasis was placed on human studies. Manual cross-referencing was also performed. Articles published in the English language within the 25 years preceding December 1999 were selected. This decision was influenced by the need to study the evolution of nutritional support in acute pancreatitis and the associated controversies. Review articles published before 1992, editorials, letters and most case reports have been excluded. Abstracts are cited only when full papers addressing a given issue are unavailable.

Need for nutritional support in acute pancreatitis

Especially in its severe form, acute pancreatitis is associated with a systemic inflammatory response causing increased metabolic demands which may progress to multiple organ dysfunction syndrome. The disease and its complications are associated with the release of proinflammatory mediators such as interleukin (IL) 1, IL-6, IL-8, tumour necrosis factor (TNF) α and platelet-activating factor[9–12]. In addition, there is activation of the complement cascade, release of oxygen-derived free radicals and nitric oxide, and generation of prostaglandin E_2, thromboxane A_2 and leukotriene$_4$ from the metabolism of arachidonic acid. If prolonged and combined with starvation, these changes lead to a rapid loss of lean body mass with its associated morbidity and death[13]. Increased intestinal permeability in animals[14–16] and humans[17], along with an associated impaired gut barrier function, may lead to translocation of bacteria and bacterial products from the gut lumen into the circulation[18]. While experimental animal work has indicated that enteral nutrition may prevent bacterial translocation in acute pancreatitis, this does not necessarily translate into a survival advantage[19].

Mass spectrometry demonstrates that total energy expenditure is 1·49 times the predicted resting energy expenditure using the Harris–Benedict equation in patients with severe acute pancreatitis[20]. There is no significant difference when patients with and without sepsis are compared. Calculation of nutrient oxidation rate suggests a high rate of protein catabolism, with increased gluconeogenesis and lipolysis. The total : resting energy expenditure ratio correlates inversely with nitrogen balance ($r = -0{\cdot}63$, $P = 0{\cdot}01$). Indirect calorimetry shows that the mean total : resting energy expenditure ratio is significantly higher in patients with acute pancreatitis complicated by sepsis than in patients with chronic pancreatitis (1·20 *versus* 1·05; $P < 0{\cdot}02$)[21]. The mean ratio for patients with acute pancreatitis without sepsis was 1·12. The same study also showed that, although 82 per cent of patients with acute pancreatitis and sepsis have a ratio above 1·10, 61 per cent of patients with non-septic acute pancreatitis and 33 per cent of those with chronic pancreatitis are hypermetabolic.

Isotope techniques demonstrate that patients with severe disease have an impaired ability to oxidize glucose compared with controls[22]. This is associated with a significantly higher urea production, indicating increased protein catabolism. This increase is not as high as predicted from nitrogen balance studies, suggesting that these patients also have diminished muscle protein synthesis. The resultant negative nitrogen balance is, therefore, a net effect of both these changes. Free fatty acid kinetics are similar in both groups. Exogenous glucose infusion causes almost complete suppression of gluconeogenesis from protein in normal subjects but not in patients with acute pancreatitis. These metabolic changes are consistent with a state of hepatic insulin resistance[23] and are similar to those observed in patients with sepsis[24].

The effects of increased metabolic demands are compounded by an inability or reluctance to maintain an adequate oral intake, so that patients become malnourished during the course of their illness. Some with alcoholic pancreatitis may also be premorbidly malnourished[25,26] and malnutrition may be especially apparent in those who have acute on chronic pancreatitis. Micronutrient and vitamin deficiencies may also be present on admission or develop during hospitalization. In addition to hypocalcaemia, which is seen in up to 25 per cent of patients with severe acute pancreatitis, deficiencies of magnesium, zinc, folate and thiamin have been described[4,27].

Severe disease usually manifests at onset or within a few days of onset[28–30] and usually follows a protracted course. On the other hand, it is common experience that mild disease resolves in less than a week. The UK guidelines[8] recommend that stratification of the severity of pancreatitis should be made within 48 h using the Glasgow score[31] and plasma C-reactive protein (CRP) level[32]. Severe disease is identified by the presence of three or more positive Glasgow criteria on both initial admission and subsequent tests over 48 h. CRP concentrations above 210 mg/l in the first 4 days of the attack have a similar predictive value[8,32]. Some authors have found that CRP concentrations reach a peak only 48 h after onset of pancreatitis[33] and others argue that concentrations above 120 mg/l may also predict severe disease[34]. The Ranson criteria[28] are popular with American workers[7] and, like the Glasgow score, three or more positive criteria indicate severe disease. The Acute Physiology And Chronic Health Evaluation (APACHE) II scoring system[35] is also useful in stratifying disease severity and has the advantage of being suitable for continuous monitoring. APACHE II scores of 8 or more indicate severe disease, but a few patients with scores of 6–7 may also have severe acute pancreatitis. Any patient who has severe acute pancreatitis, defined by any of the above scoring systems, should be considered for nutritional support.

Physiology of exocrine pancreatic function and the need for pancreatic rest

The secretions of the exocrine pancreas total 1–2 litres per day and the normal response to a meal contains twice the minimal enzyme requirement for normal digestion[36]. There is, therefore, some redundancy in the system. Recently, it has been shown that protein energy malnutrition is associated with gross reduction in pancreatic enzyme secretion and that this is restored to normal as body tissue is regained during refeeding[37]. The electrolyte-rich pancreatic juice is iso-osmotic with plasma and contains a number of digestive enzymes that include inactive zymogenic proteolytic enzymes and active amylase and lipase. Pancreatic secretions are under complex neurohumoral control and, as with other gastrointestinal secretions, have a cephalic, gastric and intestinal phase. The release of digestive enzymes is mainly under the control of cholecystokinin and vagal cholinergic stimulation, while vasoactive intestinal polypeptide influences bicarbonate secretion. Pancreatic polypeptide, calcitonin gene-related peptide, peptide YY, somatostatin and neuropeptide Y have inhibitory effects[38,39].

The concept of pancreatic rest stems from the belief that stimulation of pancreatic exocrine function in patients with acute pancreatitis releases large quantities of proteolytic enzymes which results in autodigestion of the inflamed pancreas and peripancreatic tissues, causing a deterioration in the patient's condition. In a study[40] of eight patients with acute pancreatitis it was found that interdigestive secretions of the exocrine pancreas, within 72 h of the onset of mild to moderate disease, were no different from those in 26 normal controls. On this evidence the authors propose early inhibition of pancreatic secretion with somatostatin in the acute phase of the illness. It can equally be argued, however, as these patients secrete normal quantities of pancreatic enzymes, that the gut should be capable of digesting nutrients given enterally into the jejunum. Still, some animal studies[41,42] suggest that both basal and stimulated pancreatic secretions are impaired in experimental pancreatitis, even before the development of major necrosis.

Oral and nasogastric feeding do, however, increase pancreatic secretion by stimulation of the cephalic and gastric phase, and it is suggested that early oral feeding may lead to recurrence of symptoms and delayed complications[43]. Although animal studies[44–46] show that 'pancreatic rest' reduces pancreatic synthetic activity and basal proteolytic and bicarbonate secretions, evidence from human studies is less certain. A retrospective review of 330 patients with pancreatitis suggests that early oral feeding predisposes to major peripancreatic infections, while prolonged nasogastric suction and avoidance of early operation reduces the incidence of these infections[47]. Randomized controlled studies[48,49] in patients with mild to moderate acute pancreatitis have, however, failed to establish the value and efficacy of fasting or nasogastric suction. The only firm conclusion that can be drawn from such conflicting evidence is that the benefit of pancreatic rest in patients with acute pancreatitis is unproven.

Effect of enteral feeding on pancreatic secretions

The presence of food in the stomach and duodenum elicits gastropancreatic and duodenopancreatic reflexes that result in stimulation of pancreatic exocrine secretions. However, these effects are not as pronounced when nutrients are delivered directly into the jejunum.

A study in dogs[50] showed that intragastric delivery of nutrients causes an increase in the volume, and protein and bicarbonate content, of pancreatic secretions compared with those in saline-infused controls. Intraduodenal feeding increases the volume of pancreatic secretions but does not affect protein or bicarbonate secretion. Other studies in dogs[51–53] also show that the intraduodenal administration of elemental diets or pure amino acid solutions significantly increases pancreatic secretions, suggesting that the amino acid content of elemental diets is responsible for the stimulatory effects. In contrast, intrajejunal delivery of nutrients is not associated with a significant change in the volume, or protein or bicarbonate content, of pancreatic secretions compared with controls[50]. These authors[50] also found in one human subject that avoidance of cephalic, gastric and duodenal stimuli by jejunal tube feeding using neutral amino acids did not result in pancreatic stimulation. They concluded that bypassing the stomach, minimizing acid secretion, plays an important role in keeping the pancreas at rest.

Pancreatic exocrine secretion is less, both in volume and enzyme content, in dogs fed orally with an elemental diet than in those fed commercial dog food[54]. However, these changes are apparent only a month after the commencement of feeding. Another canine study[55], in which an elemental diet was fed into the proximal jejunum, demonstrated a brisk pancreatic secretory response. However, the pancreatic juice collected was watery and enzyme poor.

A study[56] on volunteers fed either an elemental diet or a food homogenate via a nasoenteral tube placed at the duodenojejunal flexure indicates that the latter has a greater stimulatory effect on the secretion of pancreatic lipase and chymotrypsin than the former. The authors suggest that this difference might be related to the greater nitrogen content of the food homogenate. Osmolality of the feeds does not seem to have an effect.

A study on a single patient with a duodenal fistula, tube-fed into the efferent limb of a gastrojejunostomy, demonstrated that although enteral feeding does not alter the volume of secretions into the duodenum there is a decrease in bicarbonate and amylase secretion, and an increase in lipase and nitrogen content of the duodenal fistula effluent[57].

Bodoky *et al.*[58] randomized 12 patients undergoing pylorus-preserving pancreaticoduodenectomy for chronic pancreatitis to receive enteral nutrition via a needle catheter feeding jejunostomy (seven patients) or parenteral nutrition (five patients). A catheter placed during operation in the pancreatic duct was used to collect pancreatic secretions. The authors believed that the disease was mainly in the pancreatic head and that the function of the pancreatic remnant was near normal. They did not find any difference in the volume of pancreatic secretions or the content of bicarbonate, protein, chymotrypsin or amylase between the two groups.

A recent study[59] compared the effects of a jejunally administered elemental diet with those of an immune-enhancing formula on exocrine pancreatic secretions after Whipple pancreaticoduodenectomy. The authors found a small but significant increase in pancreatic enzyme and bicarbonate secretion after jejunal feeding compared with the fasting state, but there was no significant difference in pancreatic enzyme output when the effects of the elemental and immune-enhancing feeds were compared.

Although there is a paucity of human studies on the effects of oral feeding and enteral nutrition on pancreatic secretion, one may reasonably conclude from available evidence from both human and canine studies that oral, intragastric and intraduodenal feeding produce a significant stimulation of pancreatic secretions. In contrast, intrajejunal feeding has much less stimulatory effect and is therefore the route of choice for enteral feeding in acute pancreatitis.

Effect of parenteral feeding on pancreatic secretions

Kelly and Nahrwold[52] compared the exocrine pancreatic secretory response to intravenous saline and parenteral nutrition in dogs with chronic gastric fistulas and found that the latter produced a small but significant increase in the mean volume of pancreatic juice (2·4 *versus* 1·8 ml per 15 min; $P < 0{\cdot}05$) with a slight increase in mean protein and bicarbonate secretions. These differences are minimal compared with the changes found in dogs receiving an intraduodenal infusion of an enteral diet. Conflicting results have been reported in canine studies[53,60] on the effects of intraduodenal *versus* intravenous amino acids and fat on pancreatic secretions. One study[53] found that, in the short term, both routes of administration stimulated pancreatic secretions. A later study[60] demonstrated that increasing doses of amino acids and fat produce increasing responses in volume, protein and bicarbonate when administered intraduodenally, but similar intravenous doses do not produce a significant change. These findings confirm those of an earlier study[61] showing that intravenous infusion of amino acids in a canine fistula model does not result in any change in volume or protein content of pancreatic secretions. All these studies[52,53,60] compared parenteral with intraduodenal feeding, which is known to stimulate the pancreas. No direct comparison has yet been made between the secretory effects of parenteral and jejunal feeding.

A case report[62] suggests that the parenteral infusion of concentrated glucose solutions produces a decrease in volume and amylase content of pancreatic secretions, while fat has the opposite effect and amino acids cause no change. Variyam *et al.*[63] have shown that parenteral amino acids do not stimulate pancreatic enzyme secretion in healthy young men. Another study[64] of pancreatic secretion in 31 normal volunteers recorded a rise in response to parenteral amino acid infusions, a fall with glucose infusions and no change with infusion of lipids alone or a mixture of all three substrates, suggesting that in normal practice parenteral nutrition has no significant effect on pancreatic secretion.

Parenteral nutrition in acute pancreatitis

Uncontrolled studies

Feller *et al.*[65] were the first to advocate intravenous hyperalimentation followed by enteral administration of an elemental diet as supportive therapy in acute pancreatitis. In an uncontrolled retrospective analysis, they showed a decrease in the overall mortality rate from 22 to 14 per cent, which they attributed to aggressive nutritional and respiratory support. Blackburn *et al.*[25] described another uncontrolled retrospective study of 11 patients who had sustained significant malnutrition secondary to severe acute pancreatitis lasting more than 14 days. Patients received parenteral hyperalimentation combined with enteral support in the form of a defined formula diet before surgical intervention. All were later operated on for control of pancreatitis-related complications with no postoperative death or significant morbidity. The authors noted a significant improvement over the 62 per cent mortality rate of Ranson *et al.*[28] in this subgroup of patients and the 60 per cent survival rate recorded by investigators from the Massachusetts General Hospital[66]. They concluded that the improved results were due to proper preoperative assessment and correction of nutritional depletion.

Goodgame and Fischer[67] retrospectively analysed 44 patients with acute pancreatitis who were treated with parenteral nutrition. They concluded that hyperalimentation should be viewed as a method of support rather than primary therapy in this disease. They found a higher incidence of catheter-related septicaemia in the early phase of acute pancreatitis and recommended that a feeding jejunostomy should be performed as a potential means for long-term nutritional management if the need for laparotomy arises. They also demonstrated that parenteral feeding can be accomplished with minimal technical or metabolic morbidity and that it may help salvage patients with prolonged gut dysfunction secondary to complications of acute pancreatitis. These authors, however, concede that the retrospective nature of this study and the absence of any true control group make definitive conclusions difficult.

Grant *et al.*[68] also analysed data retrospectively on 121 patients with severe pancreatitis (73), chronic pancreatitis (23) and pancreatic cancer (25) who received parenteral nutrition. They found that it had no impact on the clinical course of pancreatic disease. The overall death rate was 20 per cent, with it being 15 per cent in patients with acute pancreatitis and 18 per cent in patients with complicated pancreatitis. As in the previous study, catheter-related sepsis in patients with acute pancreatitis or its complications was significantly commoner than in all other patients receiving similar nutrition in the same institution during the same time period. Although nutritional status can be maintained with few metabolic or technical complications and is well tolerated, these authors concluded that it has no significant impact on the clinical outcome of pancreatic disease.

Robin *et al.*[69] retrospectively analysed 156 patients with acute pancreatitis who received parenteral nutrition over a 3-year period. They divided the patients into two groups: group I with uncomplicated acute pancreatitis (70) and group II with local complex disease (pseudocyst, abscess or necrosis) (86). The mean Ranson score was below 3 in both groups, although more patients in group II tended to have more than three positive Ranson criteria. The duration of parenteral nutrition was significantly longer in group II. The mean durations from hospital admission to institution of a liquid oral and full oral diet were significantly less in group I. However, the number of days spent in the intensive therapy unit was similar in both groups. Mean hospital stay was significantly shorter for group I. Metabolic and electrolyte abnormalities and the requirement for exogenous insulin were significantly higher in group II. Patients with acute on chronic pancreatitis were more likely to be malnourished. The authors did not find a higher overall rate of catheter-related sepsis and attributed this to the shorter duration of therapy. They concluded that lack of specific benefit in the treated group, compared with a random group of ten patients with similar disease who did not receive parenteral nutrition, means that there is no role for parenteral nutrition in the routine management of uncomplicated acute pancreatitis. However, they recommend early aggressive parenteral feeding for patients with complications or underlying malnutrition.

Guillou[70] proposed that the increased incidence of septic complications in patients with acute pancreatitis receiving parenteral nutrition may be a result of a complex interaction of factors which include deranged gut barrier function, impaired complement fixation due to hyperglycaemia resulting from glucose/lipid-based parenteral feeding, the immunosuppressive effect of some lipids and even the fact that pancreatitis may produce an immunosuppressive state.

Kalfarentzos *et al.*[71] published their retrospective findings in 67 patients with severe disease who had three or more Ranson criteria. They divided their patients into two groups: patients in group A (38) received parenteral nutrition within 72 h of admission and in group B (29) it was delayed until after 72 h. These authors failed to show any alteration in the disease process itself. However, there was a significantly lower morbidity (24 *versus* 96 per cent) and mortality (13 *versus* 38 per cent) rate for patients in group A compared with group B. There was also a significantly higher rate of catheter-related sepsis in patients with severe acute pancreatitis compared with that in other groups of patients receiving parenteral nutrition. Pseudocysts and pancreatic fistulas also resolved with this regimen. Parenteral feeding, therefore, may be considered safe and effective in maintaining and improving the overall nutritional status of such patients; it appears to be associated with a reduction in local complications and mortality rate.

Sitzmann *et al.*[26] prospectively studied 73 patients with severe acute pancreatitis who received early parenteral feeding. Patients were divided into three groups depending on their ability to tolerate glucose-based (44), lipid-based (20) and lipid-free (nine) nutrition. Most achieved positive nitrogen balance and improved nutritional indices within 2 weeks of commencement of parenteral nutrition. There were nine deaths with a significantly higher mortality rate among patients who did not receive fat as a calorie source. Furthermore, this trend was also apparent in patients who were in negative nitrogen balance and who had a Ranson score of 3 or more.

Controlled studies

Sax *et al.*[72] carried out the only randomized controlled trial of the effects of early parenteral nutrition *versus* no feeding in 54 patients with acute pancreatitis (*Table 1*). Their patients had an average Ranson score of 1 and received either conventional treatment alone or conventional treatment with parenteral feeding within 24 h of admission. Patients with acute pancreatitis had a significantly higher rate of catheter-related sepsis than other groups treated with parenteral feeding in the same hospital (10 *versus* 1 per cent). Parenteral nutrition did not affect the number of days to oral intake, total hospital stay or number of complications

Table 1 Summary of randomized controlled trials of nutritional support in acute pancreatitis

Reference	Inclusion criteria	Study groups	Main outcome measures	Results
Sax *et al.*[72] (1987)	Patients with acute pancreatitis	Early parenteral nutrition ($n=29$) *versus* conventional therapy with no nutritional support ($n=25$)	Days to oral intake, total hospital stay and number of complications of pancreatitis	No advantage of parenteral nutrition
McClave *et al.*[73] (1997)	Patients with acute pancreatitis or acute on chronic pancreatitis with abdominal pain and raised lipase and amylase	Enteral ($n=16$) *versus* parenteral ($n=16$) nutrition. Two patients randomized twice on separate admissions	Days to normal amylase and to oral diet, length of ITU and hospital stay, nosocomial infection rate, mortality rate and cost	Enteral nutrition group fared better; the only statistically significant difference was in cost (enteral cheaper)
Kalfarentzos *et al.*[34] (1997)	Glasgow score ≥ 3 or APACHE II score ≥ 8 or CRP > 120 mg/l or grade D or E Balthazar CT criteria[74]	Enteral ($n=18$) *versus* parenteral ($n=20$) nutrition	Complications, length of ITU and hospital stay, duration of ventilation and cost	Enteral nutrition well tolerated. Patients receiving enteral nutrition had fewer septic ($P<0{\cdot}01$) and total ($P<0{\cdot}05$) complications. Cost of parenteral nutrition was three times greater
Windsor *et al.*[75] (1998)	Patients with serum amylase > 1000 units/l (stratified for Glasgow score ≥ 3 and < 3)	Enteral ($n=16$) *versus* parenteral ($n=18$) nutrition	APACHE II score, CRP, SIRS, sepsis, MODS, hospital stay, death	APACHE II score and CRP significantly decreased in enteral group but no change seen in parenteral group at 7 days. No change in Balthazar CT criteria in either group. SIRS, sepsis, MODS, hospital stay and mortality rate better in enteral group (*P* not significant)
de Beaux *et al.*[76] (1998)	Glasgow score ≥ 3	Conventional parenteral ($n=7$) *versus* glutamine-enhanced parenteral ($n=7$) nutrition	DNA synthesis and proinflammatory cytokines (TNF, IL-6 and IL-8)	Trend for glutamine group to have improved lymphocyte proliferation and reduced IL-8 release (*P* not significant)
Powell *et al.*[77] (1999)	Glasgow score ≥ 3 or APACHE II score ≥ 7	Enteral ($n=13$) *versus* no nutritional support ($n=14$)	Tolerance of enteral nutrition, intestinal dysfunction, change in inflammatory markers, organ dysfunction score	No evidence of improved outcome with enteral nutrition

ITU, intensive therapy unit; APACHE, Acute Physiology And Chronic Health Evaluation; CRP, C-reactive protein; CT, computed tomography; SIRS, systemic inflammatory response syndrome; MODS, multiple organ dysfunction syndrome; TNF, tumour necrosis factor; IL, interleukin

of pancreatitis. Patients with a Ranson score of 2 or more took longer to achieve an adequate oral intake than those with a score of 0–1 and early use of parenteral feeding did not appear to improve the eventual outcome. The authors suggest that the use of parenteral nutrition should be reserved for patients with a prolonged period of fasting or for the treatment of specific complications, such as pseudocyst or ascites.

Special formulations for parenteral nutrition

The use of intravenous lipid formulations in patients with acute pancreatitis remains controversial despite evidence that they are not harmful. Van Gossum *et al.*[78] published a retrospective experience with lipid-associated parenteral nutrition in 18 patients with severe acute pancreatitis. They showed, not surprisingly, an increased mortality rate in patients with higher Ranson scores. Furthermore, the requirement for various energy substrates and insulin was dictated by disease severity. Persistent hypertriglyceridaemia, hyperglycaemia, hypoalbuminaemia and higher insulin requirements predicted a poor prognosis.

Silberman *et al.*[79] retrospectively reviewed 11 patients with acute pancreatitis who received lipid-based parenteral feeding. All patients showed improvement or no change in serum amylase concentrations during such feeding and urinary diastase concentrations improved in the majority. There was no major change in serum lipid profile in any patient and nutritional indices either improved or were maintained in all. They concluded that lipid-based formulas are safe and nutritionally effective but do not affect the natural history of the disease. Although intravenous lipids are usually safe and well tolerated when given at the recommended rate, there are case reports in which lipid infusions were the cause of pancreatitis, presumably because of the resultant hypertriglyceridaemia[80–82]. It may therefore be recommended that hypertriglyceridaemia (greater than 4 g/l) should be avoided when lipid infusions are used in acute pancreatitis[83], and that lipid clearance should be monitored by measurement of plasma triglycerides after feeding.

Enteral nutrition in acute pancreatitis

Uncontrolled studies

The concept of enteral nutrition in patients with acute pancreatitis goes back to the 1970s when Voitk *et al.*[84] demonstrated the beneficial effects of an elemental diet in six patients with closure of fistulas, resolution of sepsis and ascites, achievement of positive nitrogen balance and weight gain. After almost two decades of dormancy stemming from the advocacy of pancreatic rest, there is now renewed interest in enteral feeding. Kudsk *et al.*[85] reviewed an experience of feeding jejunostomies in 11 patients who underwent exploratory laparotomy for complications of pancreatitis. Two died, but the remaining nine patients gradually improved on enteral feeding with none showing any increase in serum amylase concentration. Glycosuria and hyperglycaemia were common, but were easily managed with insulin. No catheters were lost and mild diarrhoea was encountered only during the first week of therapy. This study shows that prolonged jejunal feeding may be provided safely in patients with severe acute pancreatitis without aggravating the disease.

Parekh *et al.*[86] showed similar beneficial effects of enteral nutrition in nine patients with acute pancreatitis in whom enteral nutrition was commenced at a mean of 11 days after admission and continued for a mean of 16 days. This not only improved nutritional status but was also accompanied by successful resolution of complications in seven of the nine patients. The authors suggest that stable patients who are unable eat benefit from enteral nutrition. Some patients in this study[86] were fed either orally or by nasogastric tube, and five of the six patients in the study of Voitk *et al.*[84] were tube-fed into the stomach without problems. In both studies, however, feeding was commenced after the acute phase of the illness, when the inflammatory process may have been subsiding. These studies therefore do not provide evidence that oral or nasogastric feeding is safe or advisable in severe acute pancreatitis.

Simpson *et al.*[87] retrospectively reviewed an experience of nasoenteral feeding in five patients with acute alcoholic pancreatitis with a mean Ranson score of 1·8. None needed parenteral nutrition and the disease and its complications resolved in all. Nakad *et al.*[88] described an experience of early enteral nutrition in severe disease using the same technique, starting 36 h after admission. One patient required parenteral feeding because of failure to achieve nutritional goals. No patient developed relapse, hypertriglyceridaemia or abnormalities of liver function, indicating that jejunal feeding can be used safely in severe acute pancreatitis without reactivation of the inflammatory process.

Controlled studies

The only randomized controlled trial of enteral nutrition *versus* conventional therapy (i.e. no nutritional support) in severe disease[77] (*Table 1*) provides no evidence of improved outcome in patients receiving nutritional support in terms of organ dysfunction score or inflammatory markers such as antiendotoxin core antibody, IL-6, TNF receptor 1 and CRP. Patients receiving enteral feeding had significantly worse intestinal function on day 4 ($P = 0{\cdot}026$). However, this phase II trial, which has as yet been published only in abstract form, involved a total of only 27 patients and the results may be attributable to the small sample size.

Parenteral *versus* enteral nutrition in acute pancreatitis

McClave *et al.*[73] conducted the first prospective randomized trial comparing early enteral nutrition with parenteral nutrition in 30 patients with mild acute or acute on chronic pancreatitis (*Table 1*). Enteral feeding was via an endoscopically placed nasojejunal tube and parenteral feeding was via a central or peripheral line, both within 48 h of admission. Efficacy was measured by the percentage of goal energy intake (25 kcal per kg per day) achieved, days to oral diet and length of hospital stay. Although enterally fed patients lagged 1 day behind the other group in achieving energy goals, this difference disappeared by the fourth day. Mean Ranson, APACHE III and multiorgan failure scores decreased in the enteral group and increased in the parenteral nutrition group, but these differences were not statistically significant. Patients in the latter group had significantly higher stress-induced hyperglycaemia over the first 5 days. There was a statistically insignificant trend towards earlier normalization of serum amylase, progression to oral diet, and decrease in hospital and intensive therapy unit stay in the enteral group compared with the parenteral group. The mean cost of parenteral feeding was four times higher than that of enteral feeding. There are some difficulties with this study, including the fact that it was restricted solely to patients with mild pancreatitis with a mean Ranson score of only 1·3 in both arms, and that it contained a group of patients with mild attacks of recurrent pancreatitis. The study, however, does provide evidence that enteral nutrition is both feasible and safe.

In another prospective randomized trial[34], comparing parenteral with enteral feeding in 38 consecutive patients with severe necrotizing pancreatitis (*Table 1*), there was no statistically significant difference between the two groups with regard to intensive therapy unit support, use of antibiotics, hospital stay and number of days of nutritional support. Nitrogen balance improved equally in both groups, but severe hyperglycaemia requiring insulin therapy was twice as frequent in the parenteral group compared with the enteral group. Total complications and septic complications were significantly more common in the parenteral group, suggesting that enteral feeding should be preferred for nutritional support in patients with severe acute pancreatitis.

Windsor *et al.*[75] recently published a randomized controlled trial of enteral *versus* parenteral nutrition in 34 consecutive patients with acute pancreatitis who had a mean Glasgow score of 2 and APACHE II score of 8. None of the patients in the enteral group needed parenteral feeding. After 7 days of nutritional support, the enteral group fared better than the parenteral group with respect to CRP concentrations and APACHE II scores (*Table 1*). Furthermore, the serum level of immunoglobulin M endotoxin core antibodies increased in the parenteral group whereas it remained unchanged in the enteral group. The total antioxidant capacity also fell in the former group and increased in the latter. There was a reduction, albeit not statistically significant, in the requirement for intensive care, incidence of intra-abdominal sepsis and multiple organ failure, need for operative intervention and mortality rate in the enterally fed group compared with the parenterally fed group. There was, however, no difference in hospital stay. The authors conclude that enteral nutrition is not only feasible, but may reduce disease severity and improve clinical and physiological parameters compared with parenteral nutrition. However, patients in the enteral group received less non-protein energy per day and it may be hypothesized that this group tended to fare better because of the superior effects of hypocaloric feeds in the acute phase of critical illness.

Role for novel substrates and immune-enhancing feeds

Novel nutrient substrates, such as glutamine, arginine, ω-3 fatty acids and nucleotides, play important roles in some critically ill patients in the maintenance of mucosal integrity and immune status[89]. Acute inflammation and injury are associated with a reduction in plasma concentrations of glutamine[90]. It is postulated that, under these circumstances, glutamine may become conditionally essential and rate limiting for gut mucosal and immune cell metabolism. Although glutamine is present in enteral feeds as a constituent of protein, its instability in solution makes it more difficult to provide in parenteral feeds unless it is added shortly before administration or as a stable dipeptide. Significantly improved survival ($P = 0{\cdot}049$) at 6 months has been demonstrated in critically ill patients receiving glutamine-supplemented parenteral feeding compared with controls receiving standard parenteral nutrition[91] but, until recently, the benefits of enteral glutamine were unproven in terms of outcome[92]. A recent study comparing a glutamine-enhanced enteral feed with a standard isocaloric, isonitrogenous enteral feed in critically ill patients has demonstrated a decreased (albeit not statistically significant) median intensive therapy unit stay and later hospital stay in the former group[93]. The authors also document a significant reduction in postintervention costs; the cost per survivor was 30 per cent less in the glutamine-fed group.

De Beaux *et al.*[76] randomized 14 patients with severe acute pancreatitis (*Table 1*) to standard parenteral feeding or isocaloric, isonitrogenous, glutamine-enriched parenteral feeding. Thirteen patients completed the study protocol and, although the patient numbers were small and there was large individual variation, there was a trend for the glutamine-fed group to show improved lymphocyte proliferation, increased T-cell DNA synthesis and decreased release of the proinflammatory cytokine IL-8. The authors feel that this improvement in immune function may have implications in the prevention of septic complications.

At present there are no available reports on the effects of immune-enhancing feeds on patients with acute pancreatitis although beneficial effects are found in other groups of critically ill patients. Randomized controlled studies of the effects of proprietary immune-enhancing enteral feeds containing arginine, nucleotides and ω-3 fatty acids (fish oil) in patients after operation and trauma demonstrate a lower rate of postoperative infections and wound complications compared with patients receiving isocaloric, isonitrogenous control feeds[94,95]. Similar studies on critically ill patients fed with treatment and control feeds of the same[96] or differing[97] energy and nitrogen content demonstrate a reduction in hospital stay and a significantly lower rate of acquired infections and morbidity in the immunonutrition group. Two recent meta-analyses[98,99] of randomized controlled trials comparing patients receiving standard enteral nutrition with those receiving commercially available immune-enhancing feeds show that, although immunonutrition has no effect on mortality rate, there is a significant reduction in infection rates, ventilator duration and length of hospital stay in these patients.

Critique of studies on nutritional support in acute pancreatitis

Most of the clinical studies of nutrition in acute pancreatitis are retrospective and include heterogeneous groups of patients with varying disease severity and sometimes patients with acute on chronic pancreatitis or exacerbation of symptoms of chronic pancreatitis; this limits the conclusions that may be drawn. This criticism of patient selection is also applicable to some of the prospective randomized trials. Moreover, in none of the randomized trials is a primary endpoint identified or a sample size and power calculation performed. The number of patients included in these studies is small and a type II error may well be the reason for apparent lack of benefit from nutritional support or of benefit from one form of nutritional support over the other. It is well known that patients with mild acute pancreatitis do not need nutritional support and addition of such patients to the trials is both a waste of resources and dilutes the results of the studies. Patients with acute on chronic pancreatitis form a distinct population group as they may be significantly malnourished premorbidly; inclusion of these patients in trials without stratification further confounds the analysis.

Parenteral nutrition has no statistically significant benefit in mild disease[72], but it may be associated with an increased incidence of catheter-related sepsis if its duration is prolonged. On the other hand, it does not have a negative effect on outcome in severe disease and provides essential nutrients. At the same time, the results of the studies claiming superiority of enteral over parenteral nutrition must be interpreted with caution, as the theoretical benefits of enteral feeding have not yet translated into improved outcome in patients with severe acute pancreatitis. Two of the studies[73,75] that included patients with mild pancreatitis show only a trend towards better outcome in patients fed enterally, while the study[34] that included only patients with severe disease demonstrates a statistically significant reduction in total and septic complications in the enterally fed group. These results contrast with those of the phase II trial[77] which was unable to demonstrate an advantage of enteral nutrition over no nutritional therapy in patients with severe disease. What is clearly demonstrated by these trials is that enteral feeding is feasible and practical in these patients, apart from being much cheaper than parenteral feeding.

Conclusions

Parenteral nutrition, including fat, is well tolerated, does not stimulate pancreatic secretion and can minimize malnutrition when gastrointestinal dysfunction is prolonged. Similarly, nasojejunal or jejunostomy feeds are well tolerated and, unlike nasogastric or nasoduodenal feeding, do not stimulate the pancreas. Like parenteral feeding, this form of nutrition may be useful in the treatment or prevention of malnutrition in patients with acute pancreatitis. This leaves two questions. First, whether or not the routine use of parenteral or enteral nutrition has benefit in terms of clinical outcome and the natural history of the disease, or whether or not artificial nutrition should be restricted to those who would otherwise suffer the consequences of malnutrition. Second, if routine nutritional support is effective, is enteral feeding better than parenteral?

At present there is no definite evidence that artificial nutritional support alters outcome in most patients with acute pancreatitis, unless malnutrition is also a problem. A diagnosis of acute pancreatitis is not, therefore, itself an indication for instituting artificial nutrition. Nevertheless, in severely affected patients who are hypercatabolic and/or unable to eat normally for more than 7–10 days, it is prudent to begin artificial nutrition either parenterally or via the jejunum, or both, in order to prevent the clinical consequences of malnutrition. In those with acute on chronic pancreatitis and who are for this or other reasons malnourished on admission, nutritional support should be introduced as early as possible. This is not a disease-specific treatment but a supportive one aimed at maintaining physiology as near normal as possible while the underlying pathology resolves.

Jejunal feeding may be preferred where practical and tolerated, although for some patients parenteral feeding may be necessary, particularly in the early stages. The establishment and maintenance of jejunal access in patients with severe disease may be problematic, and it may be difficult to achieve the targeted intrajejunal nutrient delivery within the first few days, not least because of impaired upper gastrointestinal motility. A combination of enteral and parenteral nutrition is therefore a reasonable way to meet metabolic demands in these patients; the amount of nutrients delivered parenterally can be progressively reduced as larger volumes are tolerated enterally[100].

Larger, well conducted trials that include only patients with severe acute pancreatitis and stratify patients for disease severity, nutritional status and aetiology of pancreatitis before randomization are needed before any conclusive statement on the benefits of nutritional support on outcome can be made.

Acknowledgements

D.N.L. was supported by a fellowship from the Special Trustees of University Hospital, Nottingham.

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Review

Hereditary pancreatitis and mutations of the cationic trypsinogen gene

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Background: Mutations of the cationic trypsinogen gene have been detected in hereditary pancreatitis. This article reviews current understanding of their function and clinical significance.
Methods: An unrestricted Medline search was conducted using the key words 'hereditary pancreatitis' and 'cationic trypsinogen'. Additional material was obtained from references cited in original papers and recently published abstracts of meetings.
Results and conclusion: Cationic trypsinogen mutations have been identified in most, but not all, families with hereditary pancreatitis. This confirms existing evidence that premature trypsinogen activation plays a central role in the pathogenesis of human pancreatitis. Patients currently clinically defined as having hereditary pancreatitis should be screened for the presence of cationic trypsinogen mutations. A subgroup of patients with non-hereditary pancreatitis may also benefit from being screened for these mutations. Patients with hereditary pancreatitis should be entered into prospective, multicentre trials investigating secondary screening for pancreatic cancer. Gene therapy for hereditary pancreatitis is beyond current technological capability but remains a future therapeutic prospect for this often debilitating condition.

Paper accepted 2 March 2000

British Journal of Surgery 2000, 87, 708–717

Introduction

The diagnostic criteria for hereditary pancreatitis have traditionally included age of onset (less than 20 years) and a history of pancreatitis in at least two close relatives. Mutations of the cationic trypsinogen gene have recently been described in this condition. This has not only revolutionized the way we understand this relatively uncommon pancreatic disease but has also provided new insight into pancreatitis of commoner aetiology. The cationic trypsinogen mutations, their proposed mechanisms of action and their relevance to commoner forms of pancreatitis are reviewed. Future directions in the management of patients with these mutations, including the possibility of gene therapy, are explored.

Trypsinogen and the pathophysiology of pancreatitis

Trypsinogen is the most abundant protein synthesized by the pancreas, reflecting its pivotal roles in protein digestion and in the activation of other digestive proenzymes. Digestive enzymes are normally secreted into the intestinal lumen in inactive form, activation being initiated by the brush border enteropeptidase, enterokinase. Trypsinogen is hydrolysed to produce a 7–10-amino acid trypsinogen activation peptide (TAP) and the active enteropeptidase, trypsin. Active trypsin is stabilized in its new conformational form and rapidly activates trypsinogen and other pancreatic enzymes[1].

A number of mechanisms protect the pancreas from autodigestion[1,2]. Mechanisms that prevent trypsin activation include: (1) the synthesis of digestive enzymes in an inactive proenzyme form, (2) physical separation of the activating enzyme, enterokinase, from the pancreas, (3) condensation of digestive enzymes in zymogen granules into dense core particles, (4) separation of zymogens from lysosomal enzymes that have the capacity to activate trypsinogen and (5) maintenance of a relatively low intracellular calcium concentration.

Mechanisms that limit the damage of activated trypsin include: (1) the cosynthesis of pancreatic secretory trypsin inhibitor (PSTI) with trypsinogen, (2) trypsin autolysis, (3) hepatic synthesis of the protease inhibitors α-1-antitrypsin and β-2-microglobulin, and (4) secretion of activated enzymes.

Controversy still surrounds the issue of the location and mechanism of the initial injury that occurs in acute pancreatitis. A major theory explaining the mechanism leading to digestive enzyme activation suggests a failure in the segregation of lysosomal hydrolases from digestive enzyme zymogens[3]. This co-localization of hydrolases and zymogens within a single organelle may explain premature digestive enzyme activation, as the lysosomal hydrolase, cathepsin B, is capable of activating trypsinogen. Alternatively, trypsinogen autoactivation may occur at any point in the secretory pathway in the presence of calcium and a reduced pH[4].

Evidence that premature trypsinogen activation plays a central role in human acute pancreatitis includes the identification of cationic trypsinogen mutations in hereditary pancreatitis and the demonstration that prophylactic treatment with the antiprotease, gabexate, reduces pancreatic damage related to endoscopic retrograde cholangiopancreatography (ERCP)[5]. The latter is reflected in a reduction in the extent, but not the frequency, of raised amylase levels, and in the frequency of pancreatic pain and episodes of acute pancreatitis.

Eight trypsinogen-like genes exist within the human β T-cell receptor locus on chromosome 7. Three non-functioning relics or pseudogenes are located at the 5′ end of the locus while a group of five trypsinogen genes, including cationic and anionic trypsinogen, are located near its 3′ end[6]. These five trypsinogen genes are highly homologous, each residing within a tandemly duplicated 10-kilobase segment and each being composed of five exons. A ninth gene (mesotrypsinogen) is on chromosome 9.

Discovery of mutations of the cationic trypsinogen gene in hereditary pancreatitis

The aetiology of hereditary pancreatitis remained obscure until recently, when modern molecular genetic techniques were applied to the problem. Linkage analysis, using microsatellite markers, established cosegregation between the disease phenotype and the long arm of chromosome 7[7–9]. Having mapped the hereditary pancreatitis gene to this locus, positional cloning using a candidate gene approach was employed, whereby genes already known to be in that region were sequenced. Within weeks, Whitcomb *et al.*[10] had identified the disease gene as cationic trypsinogen. A single guanine (G) to adenine (A) transition mutation (R117H) was identified in the third exon of cationic trypsinogen that resulted in an arginine (CGC) to histidine (CAC) substitution at amino acid residue 117, using the chymotrypsinogen numbering system for serine proteases. Such rapidity of progress was made possible by the availability of large-scale genomic sequence data, demonstrating the utility of DNA sequencing projects for aiding in the positional cloning of inherited disease gene alleles. A second mutation in cationic trypsinogen was subsequently discovered in two affected families without the R117H mutation[11]. A single A to thymine (T) transversion mutation (N21I) was identified in exon 2 which resulted in an asparagine (AAC) to isoleucine (ATC) substitution at amino acid 21. These mutations have since been classified as protein serine 1 (PRSS1) allelic variants 276000.0001 (PRSS1, ARG117HIS) and 276000.0002 (PRSS1, ASN21ILE)[12]; they have been identified in families with hereditary pancreatitis from France[13], Germany[14,15], the UK[16,17], the USA[18,19] and Japan[20].

Additional mutations have been identified during the course of these studies. A cytosine (C) to T missense mutation (A16V) has been identified in exon 2 that leads to an alanine (GCC) to valine (GTC) substitution at codon 16[15]. This mutation affects the first amino acid of the trypsinogen molecule and thus directly the cleavage site of the signal peptide (*Fig. 1*). Ferec *et al.*[13] have recently claimed three novel mutations. In exon 2, an A to G transition at codon 23 results in a lysine (AAG) to arginine (AGG) substitution at amino acid residue 23 (K23R), and an A to T transversion results in an asparagine (AAC) to isoleucine (ATC) substitution (N29I). In the promoter region, a deletion of three bases, TCC at position −28, was discovered. It is noteworthy that the R117H and N21I mutations were described using the chymotrypsinogen numbering system, based on alignment of cationic trypsinogen with chymotrypsinogen at serine 195. In contrast, the A16V and the mutations described by Ferec *et al.* number the position of the amino acids by beginning at the ATG initiation codon. Correcting for this anomaly, the N29I mutation is identical to that previously described as N21I, and not a novel mutation as claimed. Adopting the recent

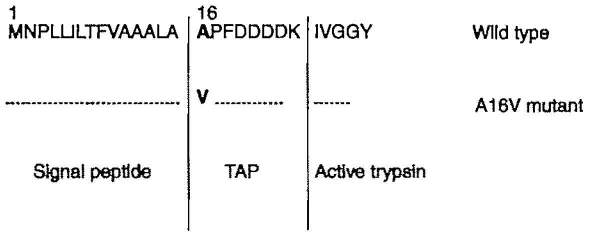

Fig. 1 N-terminal amino acid sequence of cationic trypsinogen in one-letter code. Numbers represent the position of amino acids beginning at the ATG initiation codon. The first line depicts wild-type and the second line the mutated sequence. This mutation affects the first amino acid of the trypsinogen molecule and thus directly the cleavage site of the signal peptide. TAP, trypsinogen activation peptide. Modified from reference 15

recommendations for a nomenclature system for human gene mutations[21] should eliminate confusion arising from different numbering systems. These state that for amino-acid based systems, the codon for the initiator methionine is codon 1. Theories relating to the functional significance of all of these mutations are considered in a subsequent section.

Genetic heterogeneity with respect to mutations of the cationic trypsinogen gene has thus been established. However, a recent study of an affected family without either the R117H or N21I mutations indicated that mutations in genes other than cationic trypsinogen might also be capable of producing hereditary pancreatitis[22]. In this family the disease phenotype was correlated with a region on chromosome 12, using genetic linkage analysis.

R117H mutation

Trypsin is a two-domain molecule with its catalytic site and specificity pocket located in a cleft between the two globular domains[1]. The specificity pocket accepts lysine and arginine residues as recognition sites. A semiflexible, arginine-containing, connecting chain connects the two domains. This arginine (amino acid 117) is the initial hydrolysis site of trypsin during autolysis. The R117H mutation results in the substitution of histidine for arginine at this site, thereby eliminating the initial hydrolysis site. Thus, active trypsin resists degradation because the initial cutting site is missing.

PSTI exists in trypsin-containing vesicles at a molar ratio of 1:5 with trypsinogen and is part of the multilayered defence against premature protease activation. PSTI alone is only able to inhibit 20 per cent of potential trypsin activity[12]. It is hypothesized that trypsin autolysis represents a 'fail-safe' or 'secondary brake' mechanism during conditions of excessive trypsinogen activation when the inhibitory capacity of PSTI is exceeded. Mutant trypsin escapes hydrolysis at the initial hydrolysis site. Autolysis is thereby prevented and trypsin is then free to activate the other digestive proenzymes, initiating pancreatic autodigestion and pancreatitis[23] (*Fig. 2*). *In vitro* experiments using an R117 mutation in rat trypsin support this hypothesis[24]. In this study, an asparagine residue was introduced in place of arginine at codon 117 by site-directed mutagenesis in the recombinant rat trypsin. While the catalytic properties of mutant trypsin were conserved, the mutation increased the stability of trypsin against autolysis due to increased resistance against tryptic attack.

N21I mutation

The mechanism whereby the N21I mutation causes pancreatitis remains uncertain. In the initial report on this mutation, Gorry *et al.*[11] speculated that, based upon the clinical similarities between the R117H and N21I phenotypes, its consequence would be to enhance autoactivation of trypsinogen, alter the binding of PSTI or impair trypsin inactivation by altering the accessibility of the initial hydrolysis site to trypsin. Predicted conformational changes in the crystallographic structure of trypsin support the last hypothesis[12]. The N21I substitution, by placing a hydrophobic isoleucine on the surface of cationic trypsin, may bring glutamate at residue 24 (E24) close enough to the initial hydrolysis site (R117) to form a salt bridge and so protect it from hydrolysis. Recent ***in vitro*** studies suggest that autocatalytic trypsinogen degradation may be an important defence mechanism against excessive trypsin generation, which is lost in hereditary pancreatitis[25,26]. Using a rat cationic trypsinogen homologue, mutations at positions 21 and 117 enhanced stability against autoactivation and proteolysis.

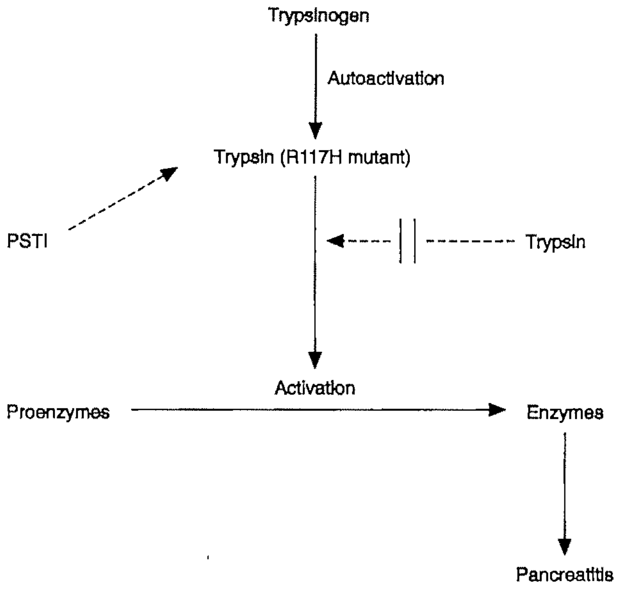

Fig. 2 Generation of active trypsin is inhibited by pancreatic secretory trypsin inhibitor (PSTI) and trypsin self-inactivation (autolysis). R117H mutant trypsin leads to pancreatitis owing to the absence of trypsin autolysis, when the inhibitory capacity of PSTI is outstripped. Dashed arrows indicate inhibitory effects. Modified from reference 10

Other mechanisms have been proposed. Secondary structure predictions of the amino acid sequences of wild-type and mutant (N21I) cationic trypsin have been made by computer analysis[20]. This showed that the N21I substitution alters the native turn structure to a sheet structure. The authors implied that this conformational alteration might impair trypsin inactivation, but this remains speculative. Others have suggested that, rather than being the cause of hereditary pancreatitis, the R117H and N21I mutations simply represent markers for a number of defects, especially ones involving the ductal system[27]. The overwhelming evidence, however, supports the view that trypsin plays a central role in the pathophysiology of hereditary pancreatitis and that these germline mutations of cationic trypsinogen are responsible for the recurrent acute pancreatitis and chronic pancreatitis observed in the clinical spectrum of the condition.

A16V mutation

The A16V mutation was discovered during the course of a study to determine the spectrum and frequency of mutations in the cationic trypsinogen gene in 44 unrelated children and adolescents with chronic pancreatitis[15]. Thirty of these patients were classified as having idiopathic disease while 14 had hereditary pancreatitis. The previously described R117H mutation was detected in one patient with the hereditary disease. A novel mutation, A16V, was present in three patients with idiopathic pancreatitis and in one patient with hereditary pancreatitis. The A16V mutation was also discovered to be present in seven first-degree relatives of these patients but only one had clinically apparent pancreatitis, indicating the low penetrance of this mutation.

This mutation leads to the exchange of an alanine for valine at codon 16. This affects the first amino acid of the trypsinogen molecule and thus directly the cleavage site of the signal peptide (*Fig. 1*). The pathophysiological mechanism whereby it induces pancreatitis is, once again, speculative. However, the authors of this report suggest that defective cleavage of the signal peptide may result in modified secretion of the preproprotein, resulting in either disturbed intracellular transport and intracellular activation or in the formation of an active trypsin instead of the inactive trypsinogen precursor. Alternatively, signal peptide cleavage may remain unaffected but conformational change of TAP may enhance trypsinogen autoactivation through increased TAP cleavage.

K23R and –28delTCC mutations

Further evidence of genetic heterogeneity in hereditary pancreatitis is derived from a recent study by Ferec *et al.*[13]. This examined 14 affected families from different regions of France, each containing at least three affected subjects. A mutation was identified in only 42 per cent of cases. This suggests that unidentified mutations may lie outside the coding sequence of the gene or that genes other than cationic trypsinogen are responsible for the occurrence of the hereditary disease in these families. Of the mutations identified in eight of the 14 families, four had R117H, two had N29I (or N21I, using the chymotrypsinogen numbering system), one had K23R and one had –28delTCC.

The authors hypothesize that the mutations found in exon 2 (N29I and K23R) alter the tertiary structure of trypsinogen and, specifically, the trypsin inhibitor binding site. If the PSTI regulatory mechanism were disrupted, excessive trypsin activity would result in autodigestion and pancreatitis. The effect of the –28delTCC is also unknown. However, as this deletion occurs in the promoter region of the gene, it might be expected that, by modifying levels of trypsinogen transcription, increased amounts of trypsin may overwhelm normal intracellular defence mechanisms, again resulting in pancreatic autodigestion.

Theories to explain how mutations of the cationic trypsinogen gene may induce pancreatitis have been presented (*Table 1*). It must be remembered, however, that none of these mechanisms have, as yet, been proven. Further work is required to confirm the functional and pathogenic relevance of these genetic alterations, especially

Table 1 Mutations of the cationic trypsinogen gene discovered to date

Reference	Year	Mutation	Nucleotide change	Amino acid change	Proposed pathogenic mechanism
Whitcomb *et al.*[10]	1996	R117H	G to A	Arginine to histidine	Eliminates the initial hydrolysis site of trypsin
Gorry *et al.*[11]	1997	N21I	A to T	Asparagine to isoleucine	Hampers access to the initial hydrolysis site of trypsin
Witt *et al.*[15]	1999	A16V	C to T	Alanine to valine	Affects the cleavage site of the signal peptide
Ferec *et al.*[13]	1999	K23R	A to G	Lysine to arginine	Alters the structure of the PSTI binding site
Ferec *et al.*[13]	1999	−28delTCC	Deletion of TCC from promoter region	None	Increased transcription of trypsinogen

PSTI, pancreatic secretory trypsin inhibitor. A, adenine; C, cytosine; G, guanine; T, thymine in human recombinant enzymes, when these become available.

New insights into hereditary pancreatitis

In 1952, Comfort and Steinberg[28] were the first to describe a family with hereditary pancreatitis. An autosomal dominant inheritance pattern, an onset of symptoms between the ages of 5 and 23 years, and the absence of known precipitating factors were the only features that distinguished it from pancreatitis of other aetiologies. Subsequent studies[29–31] have confirmed these observations and determined that the penetrance, i.e. the fraction of patients with the mutation that express the disease, is 80 per cent.

Konzen *et al.*[32] compared the two distinct forms of pancreatitis that occur in children: hereditary and idiopathic pancreatitis. Over a period of 30 years, 42 patients with hereditary and 28 with idiopathic pancreatitis were followed up. The former patients seemed to present at a younger age, and had more frequent complications and surgical interventions than those with idiopathic pancreatitis. Although standard diagnostic criteria were used, it should be remembered that this study predated the discovery of cationic trypsinogen mutations. The natural history of hereditary pancreatitis has also been compared with that of alcoholic chronic pancreatitis[33]. Twelve patients with hereditary pancreatitis were followed up for a mean duration of 15·8 years and compared with 122 patients with alcoholic chronic pancreatitis with a mean follow-up of 7·5 years. Apart from an earlier age of onset and a significant delay in diagnosis, patients with hereditary disease had a natural history similar to that of patients with alcoholic chronic pancreatitis.

Clinical characteristics of some patients known to have cationic trypsinogen have now been reported, enabling comparison of clinical features to be made between those with different mutations. In a questionnaire-based study, 28 affected members of a family with the R117H mutation were compared with 15 affected members of a family with the N21I mutation[11]. Age of onset was significantly later in the latter family. In addition, disease severity was significantly milder in the family with the N21I mutation, as assessed by the number of affected family members with more than five hospital admissions for pancreatitis. The finding that families with the N21I mutation appear to have a relatively later age of disease onset was confirmed in a recent study from Japan[20] but the number of patients with each mutation was small. At present, despite the apparent phenotypic differences between these two mutations, a distinction based on clinical features alone is not possible.

New insights into acute and chronic pancreatitis

The identification of cationic trypsinogen gene mutations in hereditary pancreatitis highlights the importance of intrapancreatic trypsinogen activation as the key event in the initiation of acute pancreatitis. Human trypsinogen has the unique property of autoactivation and this, combined with a high calcium environment, mimics the autolysis-resistant behaviour predicted for R117H and N21I mutant trypsin[12]. The cationic trypsinogen mutations strongly reinforce the existing evidence that acute pancreatitis begins within the acinar cell and that it involves premature trypsinogen activation[3].

No single theory exists to explain the morphological and clinical evolution of chronic pancreatitis. Theories of pathogenesis focus on ductal obstruction, the toxic effects of alcohol and its metabolites, oxidative stress, the necrosis–fibrosis sequence and immunopathogenic processes[34,35]. A recent attempt to synthesize the various hypotheses into a unifying model for understanding the pathogenesis of chronic pancreatitis argued that two discrete events working together are required for expression of this disease to occur[36]. The first event is inhibition of ductal bicarbonate secretion owing to a functional or structural defect. The second event is a perturbation in acinar cell function, resulting in the premature activation of digestive enzymes within the pancreatic parenchyma. Factors such as sphincter of Oddi dysfunction or ischaemia may be more important in perpetuating rather than initiating the inflammatory process.

The question of whether recurrent attacks of acute pancreatitis may lead to chronic pancreatitis remains controversial. Although alcoholics can present with what appears to be acute pancreatitis, this may instead represent a flare-up of chronic disease. The necrosis–fibrosis hypothesis suggests, however, that chronic pancreatitis is the result of repeated episodes of acute pancreatitis. Some evidence exists to support this, most notably a recent long-term, prospective clinicomorphological study of 73 patients treated for alcoholic chronic pancreatitis[37]. The histological data presented in this study revealed that the morphological features of acute pancreatitis (i.e. necrosis and/or postnecrotic pseudocysts) predominate in early stages while severe fibrosis, paralleled by deteriorating pancreatic function, was characteristic of late alcoholic chronic pancreatitis.

The transition from acute to chronic pancreatitis is well defined in the hereditary disease[11,29,30]. This provides strong support for the necrosis–fibrosis hypothesis and indicates that the primary pathogenic event in chronic pancreatitis occurs at the level of the acinar cell, rather than the ductal cell. Whitcomb[12] has recently expanded upon the necrosis–fibrosis theory, incorporating insights gained from the discovery of cationic trypsinogen mutations and new data concerning pancreatic stellate cells. This sentinel acute pancreatitis event hypothesis proposes that an episode of acute pancreatitis of sufficient severity to attract circulating monocytes to become resident tissue macrophages is a necessary first step in the development of chronic pancreatitis. Recurrent acinar cell injury, either through ethanol or ischaemic oxidative stress or recurrent episodes of acute pancreatitis, results in cytokine and chemokine release, which stimulates the resident macrophage population. Release of transforming growth factor β by these macrophages causes the infiltration, differentiation and proliferation of stellate cells. Fibrosis is the hallmark of chronic pancreatitis and stellate cells have recently been identified as a highly fibrogenic cell type within the pancreas, capable of producing the extracellular matrix components collagen types I and III and fibronectin[38]. Thus, according to the sentinel acute pancreatitis event hypothesis, it is the coexistence of pancreatic tissue macrophages, stellate cells and ongoing acinar cell injury that is responsible for the initiation and progression of chronic pancreatitis.

New insights into pancreatic cancer

Pancreatic cancer is the most serious complication of chronic pancreatitis. Before considering the risk of pancreatic cancer in hereditary pancreatitis, studies examining this risk in non-hereditary disease will be described. A multicentre historical cohort study of 2015 patients with chronic pancreatitis from six countries demonstrated a significantly increased risk of pancreatic cancer[39]. After excluding patients given a diagnosis of pancreatic cancer within the first 2 years of follow-up in order to eliminate a misclassification bias (i.e. attributing a diagnosis of chronic pancreatitis to those who may truly have had pancreatic cancer), 1552 patients remained. In this group, there were 29 cases of histologically confirmed pancreatic cancer. The expected number, derived from published, age-stratified, sex-specific and country-specific data on the incidence of cancer, was 1·76. This yielded a standardized incidence ratio (SIR), i.e. the ratio of observed to expected pancreatic cancers, of 16·5. The cumulative incidence of pancreatic cancer was 1·8 per cent 10 years after diagnosis of chronic pancreatitis and 4·0 per cent at 20 years. A detection bias, whereby increased surveillance of patients with chronic pancreatitis makes it more likely for pancreatic cancer to be detected than in the general population, may account for some of the large excess of pancreatic cancer observed. Such methodological problems may account for this SIR not being replicated in subsequent studies. A population-based cohort of 7956 Swedish patients with at least one discharge diagnosis of pancreatitis was monitored to evaluate the relationship between various clinical types of pancreatitis and pancreatic cancer[40]. After excluding the first 2 years following first discharge for pancreatitis, a SIR of 2·2 was observed. A SIR of 3·8 and of 4·8 was observed for those with chronic pancreatitis and recurrent acute or unspecified pancreatitis respectively. In addition, this modest excess risk persisted only up to 10 years after discharge, in contrast to the near-linear increase in cumulative risk of pancreatic cancer observed in the previous study. Hereditary pancreatitis was not analysed separately in either study.

The International Hereditary Pancreatitis Study Group (IHPSG) has subsequently investigated the risk of pancreatic cancer in patients with the hereditary disease[41]. A historical cohort of 246 patients from ten countries, thought to have hereditary pancreatitis as the most likely diagnosis, was followed up for a mean duration of 14·6 years. Compared with an expected number of 0·15, eight pancreatic adenocarcinomas developed, yielding a SIR of 53·3. The estimated cumulative risk of pancreatic cancer to age 70 years in patients with hereditary pancreatitis approached 40 per cent. Unexpectedly, for patients with a paternal inheritance pattern, this risk was approximately 75 per cent. Even adding two recently reported patients with pancreatic cancer who had a maternal inheritance pattern[42], this finding retains statistical significance. None the less, genetic counselling about the risk of pancreatic cancer should include patients who have inherited their defective gene from their mother. Biases that might lead to a spuriously high risk of pancreatic cancer in this study include detection bias, centres with cases of pancreatic cancer being more likely to join the study than centres without, and underestimation of pancreatic cancer in the background population. Additional analyses were performed in an attempt to eliminate some of these biases. The results remained highly statistically significant. In patients with hereditary pancreatitis, smoking is an additional risk factor that more than doubles the already high risk of pancreatic cancer[43]. In addition, those who smoke develop pancreatic cancer 20 years earlier than non-smokers.

Preliminary observations from the Midwest Multicentre Pancreatic Study Group (MMPSG) appear to indicate that the risk of pancreatic cancer was not overestimated in the IHPSG study[44]. Assuming that only those mutation-positive patients who have developed chronic pancreatitis are at risk, then the five cancers observed in 20–30 individuals at risk are consistent with the level of risk determined by the IHPSG.

Despite conflicting results concerning the magnitude of the SIR of pancreatic cancer in pancreatitis, two findings clearly emerge from these studies. First, chronic pancreatitis is a significant risk factor for the development of pancreatic cancer. This may be a consequence of the prolonged inflammatory microenvironment in the pancreas, analogous to the increased risk of colon cancer in longstanding ulcerative colitis. Second, the SIR of pancreatic carcinoma observed in hereditary pancreatitis appears to be significantly higher than that observed for pancreatitis of other aetiology. Reports from the MMPSG[44] suggest that only hereditary pancreatitis family members with prolonged chronic pancreatitis are at risk for pancreatic cancer. Furthermore, the occurrence of pancreatic cancer is not mutation specific as it occurs in families with the R117H mutation, the N21I mutation and in families negative for both. Thus it appears that the risk of pancreatic cancer in the hereditary disease is related to the longstanding duration of pancreatitis in these individuals rather than to the cationic trypsinogen mutation.

Based on the findings above, some authorities recommend screening the high-risk group, represented by those with hereditary pancreatitis over the age of 50 years, for pancreatic cancer. The problem is that no good screening investigation for pancreatic cancer is available for *any* group. Current serological tests and tumour markers lack sensitivity and specificity. Radiological tests are expensive and involve exposure to ionizing radiation. Endoscopic techniques, particularly ERCP, are associated with morbidity and death. Optimal screening strategies are currently being debated and a number of prospective, multicentre trials have been established.

Are cationic trypsinogen mutations present in non-hereditary pancreatitis?

The issue of whether or not patients with pancreatitis due to the commoner aetiologies possess cationic trypsinogen mutations is highly relevant. First, it may provide new understanding of the pathogenesis of pancreatitis in these groups. As only about 5 per cent of all alcoholics develop chronic pancreatitis, there are clearly cofactors, genetic or environmental, that determine individual susceptibility to alcoholic chronic pancreatitis. Investigation into the role of genetic susceptibility is still in its infancy, but mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene[45,46] and polymorphisms of cytokine[47] and ethanol-metabolizing enzyme[48] genes have been associated with susceptibility to pancreatitis. It is likely that expression of the pancreatitis phenotype is influenced by the possession of a range of susceptibility genes and cationic trypsinogen may be one such gene. Second, it may turn out in the future that the clinical management of hereditary pancreatitis will differ from that of pancreatitis of other aetiology, in terms of both screening for pancreatic cancer and potential gene therapy. Consequently, accurate identification of *all* those who may benefit is paramount. Re-examination of all patients previously classified as having idiopathic or alcohol-induced disease may be necessary in order that no-one is denied the benefits of an accurate diagnosis, a more accurate prognosis and an altered management that may, one day, include a cure for this condition. Reclassification may be possible on clinical grounds, through the retaking of a detailed history, emphasizing age of onset of symptoms and family history of not just pancreatic disease but also diabetes mellitus and unexplained abdominal symptoms[17]. However, it is unlikely that clinical grounds alone will form the sole basis for altering the diagnosis. The advent of molecular biology techniques that afford an easy means of screening large numbers of patients for mutations is likely to have an important future role in identifying patients who may have been previously incorrectly labelled. Consequently, studies are required to determine whether cationic trypsinogen mutations occur in cases of non-hereditary pancreatitis and with what frequency. Only then will it be possible to determine whether these mutations are likely to have a significant pathogenic role in such conditions, and the existence and extent of the problem of failing to identify those who may truly have hereditary disease.

Screening for cationic trypsinogen mutations in non-hereditary pancreatitis has been undertaken in a number of studies. The presence of the R117H and N21I mutations has been sought in one study of 35 patients with alcoholic chronic pancreatitis[49] but neither mutation was detected in this group. A similar study also failed to identify either the R117H or N21I mutation in 48 patients with alcoholic chronic pancreatitis but did detect one R117H mutation among 16 patients with idiopathic juvenile chronic pancreatitis[50]. Cationic trypsinogen mutations have been identified in two patients with a family history of only one relative with pancreatitis, and in one patient whose family history included diabetes mellitus and chronic undiagnosed abdominal pain but did not specifically include pancreatitis[17]. The problem of patients with hereditary disease being incorrectly labelled was highlighted by this study, as nine of 48 patients referred to a pancreatic clinic with a presumed diagnosis of idiopathic chronic pancreatitis were found to have cationic trypsinogen mutations. The R117H mutation has also been detected in five of a group of 41 patients with a clinical definition of idiopathic pancreatitis[51]. Three of these patients had only one family member with a history of pancreatitis, one had a relative with pancreatic cancer and one had no relatives with pancreatic disease. The authors' group has reported the detection of the same mutation in a patient labelled for 20 years as having alcoholic pancreatitis and with no family history of pancreatic disease[52]. Witt *et* *al.*[15] have described the A16V mutation in three patients with idiopathic pancreatitis and in one patient with hereditary pancreatitis, during the course of a study to determine the spectrum and frequency of mutations in the cationic trypsinogen gene in 44 unrelated children and adolescents with chronic pancreatitis. Thirty of these patients were classified as having idiopathic disease while 14 had hereditary disease. The A16V mutation was also discovered in seven first-degree relatives of these patients but only one had clinically apparent pancreatitis, indicating the low penetrance of this mutation. The strong association of these mutations with idiopathic chronic pancreatitis has led some authors to conclude that genetic testing for mutations in the cationic trypsinogen gene should be included in the diagnostic evaluation of patients with chronic pancreatitis, even in the absence of a positive family history.

Tropical pancreatitis is a non-alcoholic form of chronic calcifying pancreatitis, concentrated within certain geographical areas of a country, that has been observed mostly in children and young adults[53]. The R117H mutation was sought among 16 Bangladeshi patients with early disease onset[54]; none was found to be positive for this mutation. Further large-scale studies aiming to detect the full range of known mutations are warranted in this form of pancreatitis whose aetiology remains obscure.

Transgenic animal models and gene therapy

Progress in pancreatitis research is hampered by the inaccessibility of the human pancreas to observation. Other obstacles include the lack of safe pancreatic biopsy techniques, difficulty in distinguishing initiating events from the concomitant inflammatory response, and the self-destructive nature of the disease process itself. A variety of animal models have been developed, but these suffer from a lack of translational impact when applied to the human condition[55,56]. The discovery that mutations in the cationic trypsinogen gene are responsible for hereditary pancreatitis, in combination with recent advances in transgenic technology, provides the opportunity to generate an animal model with a pathogenic mechanism that mimics human disease. Coupling of enhancer/promoters to wild-type and mutant cationic trypsinogen-encoding complementary DNAs should produce a construct capable of selective transgene expression in acinar cells, with the potential for spontaneous and/or inducible development of acute pancreatitis[57]. The development of a model that mimics human pancreatitis, with high translational potential, may prove to be one of the most important advances deriving from the discovery of cationic trypsinogen mutations.

Hereditary pancreatitis has attracted attention as a possible model for future gene therapy. An effective delivery system that results in directed, appropriate and persistent protein expression within the pancreatic acinar cells has yet to be developed. If and when such delivery systems become available, strategies to overcome the problems presented by the pathophysiology of hereditary pancreatitis will be necessary. As this is an autosomal dominant disease, inserting a new copy of the wild-type gene would be ineffective. One solution is to produce a homologous recombination to repair the point mutation[1]. This has already been attempted in sickle cell anaemia, using a chimeric RNA–DNA oligonucleotide to correct the mutation in the haemoglobin B-S allele[58]. Alternatively, a gene for PSTI, under an inducible promoter, might be introduced[23]. PSTI could then be driven to be produced at molar ratios of 1 : 2 or 4 : 5 to trypsinogen instead of the usual 1 : 5. This should raise the threshold for inappropriate intracellular trypsin activation. Although purely speculative at this time, gene therapy offers the exciting prospect that, one day, an effective treatment for hereditary pancreatitis may be achieved.

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Review

Fournier's gangrene: a review of 1726 cases

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Background: Although there is much consensus, certain controversies exist regarding the management of Fournier's gangrene.

Method: Publications in English on Fournier's gangrene from January 1950 to September 1999 were obtained through the Medline database and relevant reference lists in publications. It was possible to identify 1726 cases for study. Data extracted for review included country of reported cases, number of patients in each report and relevant clinical features.

Results: Fournier's gangrene occurs worldwide. However, its definition has generated considerable controversy as efforts are made to refine the original description in the light of increasingly understood aetiological factors. Attempts to classify the disease into primary and secondary forms have not been successful. The basic pathological process, necrotizing fasciitis, has been identified in the perineum of women and children, although the disease afflicts the male more often than the female. Most reported cases have occurred in the USA and Canada. The major sources of sepsis are the local skin, colon, anus and rectum, and the lower urinary tract. Colonic, anal and rectal sources carry the worst prognosis. Diabetes mellitus is important in aetiological terms. Rare causes include vasectomy and circumcision. Investigations are essential to define the cause of an episode but not for the diagnosis of the disease. Early aggressive treatment of Fournier's gangrene and underlying conditions is essential. Hyperbaric oxygen and honey are treatment modalities yet to be universally adopted. Risk of death, 16 per cent overall in this series, is related to the patient's condition at presentation.

Conclusion: Controversies over the definition of Fournier's gangrene persist but these do not affect the treatment options. The diagnosis is made on clinical grounds. The occurrence of the disease in women is under-reported and may go unrecognized by some clinicians. Some treatment options, such as hyperbaric oxygenation and radical excision, remain controversial.

Paper accepted 2 March 2000

British Journal of Surgery 2000, 87, 718–728

Introduction

The disease eponymously credited to Professor Jean-Alfred Fournier (1832–1914), a Parisian dermatologist and venereologist, had been reported in 1764 by Bauriene[1]. King Herod the Great of Judaea is suspected to have been afflicted by it in association with diabetes mellitus[2]. The famous Persian physician Avicenna described the same disease in 1877[3]. Fournier in 1883, however, was the first to describe the condition in a specific region of the body, namely the scrotum. He used the term 'fulminant gangrene' of the penis and scrotum[4] and his description was based on five young men with scrotal gangrene. The cardinal points of that description[5] included: (1) sudden onset in a hitherto healthy young man, (2) rapid progression to gangrene and (3) absence of a definite cause.

Over the years, several terms have been applied to Fournier's gangrene. Meleney in 1924, while in China, described a more generalized form of the disease and termed it 'streptococcus gangrene'[6], and Wilson coined the term necrotizing fasciitis in 1952[7]. Other terms applied to Fournier's gangrene include periurethral phlegmon[8], phagedena[9] and synergistic necrotizing cellulitis[10,11]. Sensationalist medical journalists have more recently dramatized necrotizing fasciitis by associating it with 'flesh-eating bacteria'[12].

The disease process affects all ages and has been reported in both sexes, but its occurrence in women appears not to be widely accepted by clinicians, especially gynaecologists. Fournier's gangrene is enigmatic to the physician and embarrassing to the patient (*Fig. 1*). Several aspects of the disease are dogged by controversy, especially definition of

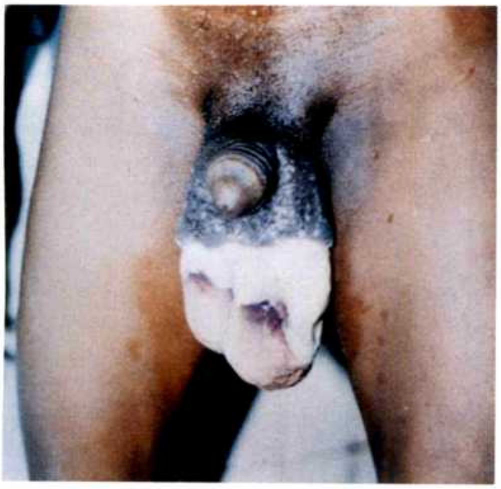

Fig. 1 Fournier's gangrene affecting most of the scrotum

the condition and prescriptions for treatment. A review of the reports on the disease in the English literature in the last half of this century is undertaken here to highlight the advances, agreements and controversies in its management.

Method

Publications in the English language from January 1966 to September 1999 were obtained through the Medline database. These were augmented with relevant citations in the reference lists of these papers. Publications from January 1950 to September 1999 with sufficient data on individual cases, including case reports, were selected for the study. Data extracted included leading authors' names, year of publication, source country of reported cases, the number of patients in each report, and clinical features including age, sex, origin of sepsis, associated illnesses (such as diabetes mellitus), anatomical distribution of gangrene, treatment procedures, complications, length of hospital stay and deaths.

Definition

Since the original description, the avalanche of aetiological factors identified has led to attempts to redefine Fournier's gangrene. Campbell in 1955[13] and Kilby in 1962[14] suggested that 'true' Fournier's gangrene should be reserved for those cases in which a portal of entry by bacteria is not demonstrable. Bahlmann *et al.*[15] advocated that the eponym Fournier should be reserved for the rare fulminating idiopathic cases while the remainder are called necrotizing fasciitis of the genitalia secondary to whatever is the underlying disease. This view was supported by Benizri *et al.*[16]. Some authors have tried to classify the condition into primary and secondary forms[15,17], primary indicating no apparent aetiology. With the increasing findings of sources of sepsis in Fournier's gangrene, Bejanga[18] suggested that this classification is unlikely to advance the course of management of the disease. Thadepalli *et al.*[19], with six of nine patients idiopathic, proposed the term polymicrobial genital gangrene to accommodate both primary (idiopathic) and secondary cases in both sexes. From another perspective it has been proposed that necrotizing soft tissue infections of the perineum should not be considered idiopathic[20]. A recent report from Nigeria has argued that Fournier's original description did not mention infection, whereas infection is now recognized to be invariably present, and has suggested that the disease should be called 'infective gangrene of the genitalia' instead of 'Fournier's gangrene'[21].

A compromise definition of Fournier's gangrene was proposed by Smith *et al.*[22] as 'an infective necrotizing fasciitis of the perineal, genital or perianal regions'. This definition includes men at all ages as well as children and women, two groups not included in Fournier's original report. Encompassing as this definition is, certain groups of genital gangrene have apparently been excluded from the category of Fournier's gangrene by some authors. Frydenberg[23], describing a case of dry gangrene of the penis in a diabetic, suggested that this was not a true Fournier's gangrene because no organisms were isolated. Perineal or genital gangrene in patients in end-stage chronic renal failure with diabetes[24,25] and with secondary hyperparathyroidism[26] has not been accepted as Fournier's gangrene by some authors. The major contention is the absence of proven infection in the presence of gangrene. However, genital gangrene in association with polyarteritis nodosa[27], vasculitis[28,29] and pyoderma gangrenosum[30] also comes into this category but has been accepted as Fournier's gangrene by the reporting authors. In some of these, the disease was unrelenting in spite of surgical resection and antibiotics, only to respond to high-dose systemic corticosteroids[29,30]; this suggests that infection was not the main problem.

Age and sex

The pathological process in Fournier's gangrene has been observed in the perineum of children[31–33] and women[34–36]. Contrary to Fournier's specification of male youth in his description of scrotal gangrene, there is an increasing age and sex mix of patients suffering from the disease[15,37]. While this may be a reflection of increasing longevity[1,38], it is interesting to note that most of the factors associated with Fournier's gangrene, such as colorectal disease, urological disease and diabetes, present later in life. Males far outnumber females, in a ratio of 10 : 1 in the 1726 cases under review. Reports including women, especially with postpartum perineal necrotizing fasciitis, are partly responsible for the apparent rising incidence of Fournier's gangrene[39].

Ethnicity and social class

Some have suggested that poor socioeconomic conditions contribute to the development of Fournier's gangrene[40,41], and alcoholism has also been incriminated[42–44]. Indeed, there may be a relationship between low socioeconomic class and alcoholism. A report from Europe has stated that the disease is 'not so frequent in our civilized world'[45], but Fournier's gangrene occurs in affluent as well as poor communities, as evidenced by the many reports from affluent regions of the USA and Europe. Regarding social class, a dental surgeon has been reported to suffer from it[46].

There have been claims that the condition is especially prevalent in Africa and Asia[47,48], and the pattern of this disease in Africa and India[18,40,49–51] differs from that in Europe and America[41,47]. Skin as the source of sepsis is more common in the developing world and the mortality rate is much lower[52]. It has been speculated, without proof, that there may be a strong resistance to infection in the negro race or that the organisms involved in Africa lack sufficient virulence for more severe sepsis[50]. This review shows that among English-speaking regions the highest incidence of the disease occurs in the USA and Canada (*Fig. 2*). However, ethnicity could not be identified in the relevant reports.

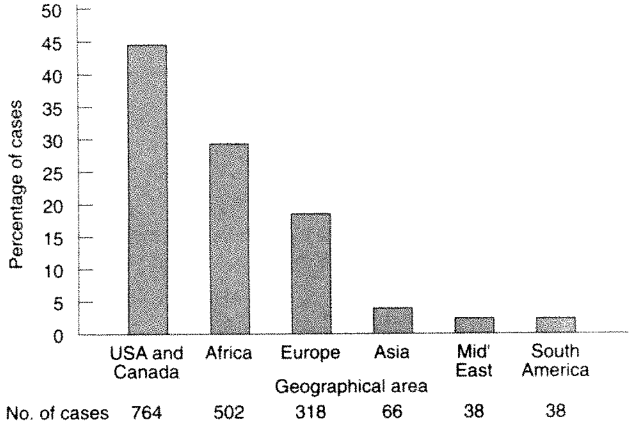

Fig. 2 Geographical distribution of 1726 cases of Fournier's gangrene reported in the English literature

Aetiology

Although the original description was emphatic about the absence of a known cause, diligent investigations have often revealed underlying pathological processes leading to perineal and genital gangrene[5,53–55]. These processes may arise from the local skin[10,18,56], the urinary tract[11,57,58] and the colorectal region[54,59,60]. Far from being idiopathic, the origin of sepsis can generally be located at one of the above three sites[16,43]. Urinary tract lesions associated with Fournier's gangrene include renal abscess[57], urethral stone[61] and urethral stricture[8,15,43,62]. Intestinal lesions are the commonest foci of sepsis and include ruptured appendicitis[63–65], colonic carcinoma[64,66,67] and diverticulitis[53,68]. The distribution of suspected sources of sepsis in the present series was dermatological 24 per cent, colorectal 21 per cent and urological 19 per cent (*Table 1*); the anatomical source was unknown in 36 per cent of the patients.

Some systemic illnesses are associated with Fournier's gangrene. The most frequent of these are diabetes mellitus, (known even in Fournier's time and seen in 10–60 per cent of cases[1,11,39,60]) and alcoholism[41,43,69]. Others are leukaemia[10,70,71] and human immunodeficiency virus (HIV) infection[21,72–74]. The common denominator in all these conditions is impaired host resistance from reduced cellular immunity[75]. Critical ischaemia and invasion by organisms normally commensal in the area then lead to gangrene[76]. The galloping rate of spread of HIV infection in Africa is a cause of concern with respect to Fournier's gangrene, as has been noted in Zambia[73]. Although Crohn's disease is associated with abscesses and fistulas, it has been reported only once in association with Fournier's gangrene[77].

There have been sporadic reports of filariasis caused by the worms *Wuchereria bancrofti*[49,78] and *Onchocerca volvulus*[79] in patients with Fournier's gangrene, and generalized scabies due to the mite *Sarcoptes scabiei* was the only

Table 1 Sources and aetiological factors in 1726 cases of Fournier's gangrene

Source/factor	No. of patients
Dermatological	417 (24)
Anorectal	356 (21)
Urological	329 (19)
Diabetes mellitus	345 (20)
Alcohol abuse	158 (9)
Total	1605 (93)

Values in parentheses are percentages. Some reports did not record the source of sepsis or aetiological factors abnormality found in one patient with the condition seen by this author. Whether the relationship between Fournier's gangrene and filariasis and scabies is causal or casual remains to be determined.

Local trauma from human bites, anal intercourse[80] and, rarely, coitus[4,81] have been associated with the disease although Fournier himself doubted a causal relationship between his eponymous illness and sexual intercourse as otherwise 'we would see a great deal of this problem in our clinics'[4]. Some antecedent events resulting in Fournier's gangrene include hernia repair[82,83], vasectomy[84,85], Thiersch operation for rectal prolapse[86], haemorrhoidal banding[87], urethral catheterization[43,88], neonatal circumcision[31,32,89], prostatic biopsy[90], use of penile prosthetic implants[91,92] and femoral puncture for splenic angiography[93]. Fish bone[56], and chicken bones in a father and his son[94], impacted in the anus have resulted in Fournier's gangrene.

Bacteriology

Infection is confirmed in the classical disease by positive bacterial culture. Many types of organism, singly or in combination, are encountered[19,54]; polymicrobial cultures of anaerobes and aerobes are the rule rather than the exception. These organisms are indigenous commensals below the pelvic diaphragm in the perineum and genitalia[5,16,60,76] and include clostridia, klebsiella, streptococci, coliforms, staphylococci, bacteroides and corynebacteria. Their synergistic opportunistic activities inflict devastating necrotizing fasciitis on the hapless patient[95]. In synergism, one bacterium produces a nutrient for another, which in turn produces a leucocidal toxin. This toxin then protects both organisms from phagocytosis. Furthermore, the aerobe by decreasing the oxygen tension produces a thriving atmosphere for the anaerobe[96].

Crepitus in gangrenous tissues gives the false impression of clostridial infection. Nevertheless, the gas-gangrene organism, *Clostridium perfringens*, has occasionally been isolated[10,97], and there is a single report of *C. tetani*[98]. There have been reports of sterile cultures even from fetid, offensive, discharging gangrene[10,16,99]. It has been speculated that this is due to poor technique in obtaining the specimen, especially for anaerobes.

Investigations

Investigation is aimed at identifying concomitant diseases to enable effective treatment. In this regard, such investigations as urinalysis, urine bacterial culture and sensitivity, cystourethroscopy, sigmoidoscopy, barium enema and tissue biopsy to identify or exclude a malignancy may be indicated[16,44,100]. Examination under anaesthesia may be required[101]. Bacteriological examination of pus is essential to identify organisms and their antimicrobial drug sensitivities. The best specimen for anaerobic culture is pus aspirated into a syringe, followed by expulsion of air if present[5]. The extent of disease in a particular patient may require investigations such as abdominal ultrasonography[102], computed tomography[65,103] and magnetic resonance imaging[104]. When scanning for intra-abdominal abscesses, a 'negative' scan should not preclude further debridement or laparotomy if these seem otherwise indicated[102].

Pathology

Fournier's gangrene is a synergistic necrotizing fasciitis, defined as a suppurative bacterial infection of the perirectal, perineal or genital area, which leads to thrombosis of small subcutaneous vessels and with infection, results in the development of gangrene of the overlying skin[13,36,76]. However, deeper extension to cause myonecrosis, which has been noted in the perineal condition[86], is not generally considered to be a feature of classic Fournier's syndrome[102]. The bacterial synergism involves the production of exotoxins whose activities result in tissue necrosis and synthesis of gases that produce the repulsive stench and crepitus, pathognomonic of anaerobic infection[5].

The extent of disease in a particular patient is variable. While only a small patch of scrotal skin may be gangrenous (*Fig. 3*), the whole scrotum may slough off (*Fig. 1*). Although

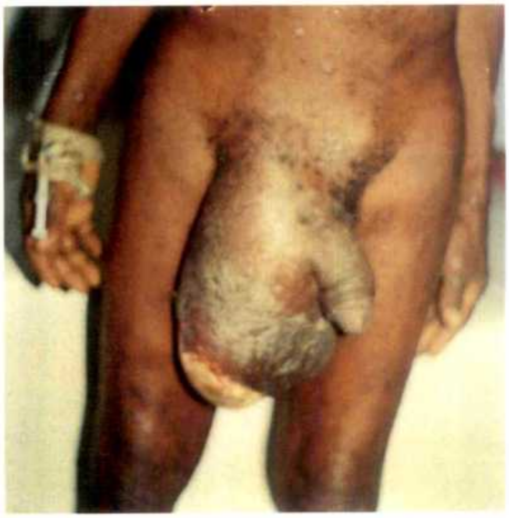

Fig. 3 Fournier's gangrene involving a patch of the right hemiscrotum containing an irreducible hernia. The patient also has scabies

the original description of Fournier was about the scrotum, the penis alone may be affected with scrotal sparing[80,100] (*Fig. 4*). Extension may reach the abdominal wall[15,16], thighs[62], chest wall and axilla[34,105]. Testicular involvement is rare. The blood supply to the scrotum comes from the pudendal arterial branches of the femoral artery[5,54], while the testicular artery is a direct branch from the aorta[54]. When testicular involvement occurs, it indicates a retroperitoneal or an intra-abdominal source of infection[55,64,68]. Testicular involvement includes orchitis and gangrene[44,64]. When the penis is involved, the corpora are usually spared while the skin sloughs off. However, synchronous thrombosis of the corpus spongiosum and cavernosum has been reported[61].

Presentation

Although the original description of scrotal gangrene emphasized a sudden onset, the presentation may be insidious[5,76,106]. There have been graphic accounts of rapid progression of the disease locally and systemically to toxicity in patients undergoing treatment[10,43,67]. Poignant descriptions of the clinical presentation include 'dirty dishwater fluid'[35] to describe the pus discharging from a Fournier's gangrene. Randall reported the 'overwhelmingly repulsive, fetid odour'[107]. He further stated that 'where the scrotum is involved, the skin, subcutaneous tissues, fascia, dartos, and all the structures of its wall, come away in a stringy, fetid mass. The testes, bared of their tunica vaginalis, hang suspended by their cords, shamefully exposed, though remarkably free of gangrene, inured and oblivious to their surroundings (or possibly I should say lack of surroundings), and can be handled freely without causing the slightest discomfort'. The testes in total scrotal gangrene may hang, bereft of cover, like the clappers of a bell.

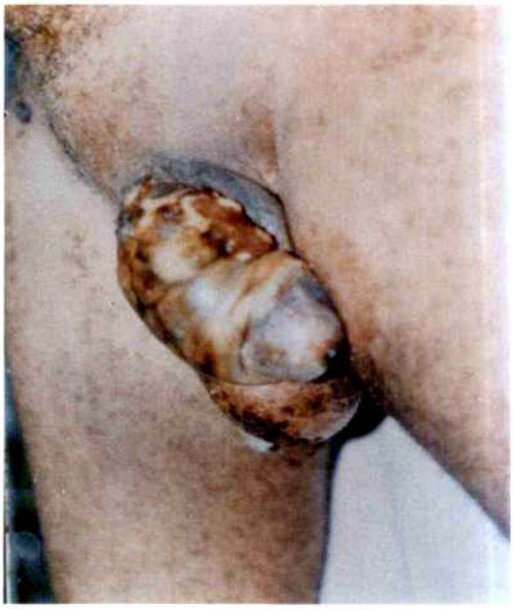

Fig. 4 Fournier's gangrene affecting only the penis and sparing the scrotum in a patient with rectal carcinoma

Identifying the source of sepsis

Efforts have been made to identify the likely source of sepsis. Tracing the anatomy of the genitoperineal region, it has been suggested that sepsis from a urinary focus spreads through the urethra to the corpora. From here a proximal spread through the inguinal canal may involve the abdominal wall, while a distal spread involves the scrotum but spares the perianal tissues[5,58]. In this hypothesis, spread from an anorectal focus extends to the perineum and then the scrotum, before involvement of the abdominal wall. However, a diabetic with a low rectal cancer, who presented with penile gangrene and rapid extension of necrotizing fasciitis through the inguinal canals to the anterior abdominal wall after commencement of treatment, has been described; the scrotum remained completely unaffected[100]. Edmondson *et al.*[108] suggest that both urethral and perirectal infections ultimately reach the superficial perineal space, thereafter to produce the same pattern of disease.

Treatment

Urgent resuscitation with fluids, which may include blood transfusion, is necessary in patients who are seriously ill[1]. The universal finding of a mixture of organisms has led to treatment with multiple antimicrobial agents targeted at three principal groups of organisms. Penicillin is recommended for streptococci, metronidazole for anaerobic organisms, and a third-generation cephalosporin (with or without gentamicin) for coliform organisms and staphylococci[16,49]. To quote Laucks: 'Empiric broad-spectrum antibiotic therapy should be instituted, regardless of Gram's stain and culture results. The antibiotic regimen chosen must have a high degree of effectiveness against staphylococcal and streptococcal bacteria, gram-negative coliforms, pseudomonas, bacteroides and clostridia'[102]. Parenteral hyperalimentation has been advocated by Baskin *et al.*[60] and Wolach *et al.*[44]. This, generally, has been found to have unacceptable side-effects. Enteral feeding is preferred and is usually sufficient to maintain a positive nitrogen balance.

The natural course of the disease involves regeneration of the scrotum once the infection and necrosis have subsided[53,107]. The scrotum has been noted to possess a remarkable ability to regenerate and heal[47,53]. There are reports of successful treatment without surgery (beyond the application of usual wound dressings)[21,32,50]. As part of conservative treatment, the use of unprocessed honey was enthusiastically advocated by Efem[51] and this has been supported by Hejase *et al.*[41].

The false impression of clostridial infection from crepitus in gangrenous tissues translated into the recommendation of hyperbaric oxygen therapy for the treatment of every case of necrotizing fasciitis[97]. Such therapy has been found effective in both clostridial and non-clostridial infections[10,69,97], and the synergism between anaerobes and aerobes in Fournier's gangrene has been used to justify the its use[109]. Hyperbaric oxygenation increases tissue oxygen tension to a level that inhibits and kills anaerobic bacteria[16,69,109], while also reducing systemic toxicity, limiting necrosis and enhancing demarcation of gangrene[97]. However, in one retrospective study of patients with necrotizing fasciitis, the results cast doubt on the advantage of hyperbaric oxygen in terms of mortality and morbidity rates[110]. Before Randall's era, orchidectomy was erroneously part of the treatment of Fournier's gangrene[107]. However, orchidectomy has occasionally been carried out owing to lack of space to house testes bereft of skin cover[1,49,85].

There is a consensus that the treatment of necrotizing fasciitis, including Fournier's gangrene, should be prompt and aggressive[16,39,43,97]. Meleney[6] introduced surgical debridement in the treatment of necrotizing fasciitis in the mid 1920s and this has remained the most successful mode of treatment. While antimicrobial agents are essential to control the multiplication and systemic spread of bacteria, prompt debridement of necrotic tissues, the nidus of the infective process, remains the basis of management of Fournier's gangrene[1,59,69]. The goal of surgical debridement is to remove all non-viable tissue, halt progression of infection and alleviate systemic toxicity[11,102]. Debridement of necrotic tissues should be repeated if necessary[55,76]. As noted by Hollabaugh *et al.*[69], 'because of the infiltrating nature of necrotizing fasciitis, multiple surgical debridements are paramount to remove any nidus of remaining infection'. Radical excision, including healthy tissue, has been advocated by some authors[6,10]. Attah even recommended excision so radical as to permit primary closure of the resulting wound[78]. The use of colostomy and catheterization in the treatment of the disease has provoked controversy: While they have been condemned by some[76], many authors advocate their application in appropriate circumstances[1,38,41,59].

Morbidity

Morbidity in Fournier's gangrene is variable and this is mirrored in the duration of hospital stay which ranges from 2 days[78] to 278 days[111]. While there are reports of spontaneous healing with dressings alone[21,32,50], there have also been pleas for the avoidance of spontaneous healing as it can lead to immobilization of the testes[13,38]. The adverse clinical consequence of such immobilization is not clear. Healing may sometimes be so complete as to leave no recognizable scars, and recurrence, although extremely rare, is not unknown[74].

Complications

Unacceptable cosmetic complications have required reconstructive procedures[48,112]. Tissue loss may be so great as to lead to the sacrifice of the testes when no suitable accommodation can be found[49,85]. Although testicular involvement is rare, testicular abscesses and gangrene complicating Fournier's gangrene have necessitated orchidectomy in a few patients[46,60,64]. Penile gangrene may result in total loss of the penis, surgically[113] or spontaneously[100]. Ketoacidosis may complicate the condition in diabetics and may be fatal[109,114]. It is interesting to note, too, that Fournier's gangrene may be the first presenting feature of diabetes mellitus[115,116]. The effect of such gangrene on fertility and libido has not received much attention. Baskin *et al.*[60] reported a single case of infertility in 29 patients. Other notable complications include fatal tetanus[98] and squamous cell carcinoma in a scar resulting from Fournier's gangrene[113].

Mortality

The mortality rate associated with Fournier's gangrene is lower than that of other forms of necrotizing fasciitis and 'probably reflects the ease with which natural and surgical drainage can occur in the lax and easily accessible scrotal and penile areas'[5]. The mortality rate in Fournier's gangrene varies from 3 to 45 per cent[41,53]. Causes of death have included severe sepsis[15,37], coagulopathy[114], acute renal failure[60,83], diabetic ketoacidosis[109,114] and multiple organ failure[55]. The overall mortality rate in the 1726 cases in this study was 16 per cent. This is higher than that found by Jones *et al.*[5] (13 per cent) and Asci *et al.*[42] (15 per cent), but lower than the 22 per cent reported by Stephens *et al.*[39]. Several contributory factors have been mentioned, most arousing some controversy. Renal failure, hepatic dysfunction and older age have a worsening effect on mortality rate[16,60], although in a study of 34 patients Asci *et al.*[42] concluded that age did not affect the progression of the disease. In a review of reports from Nigeria, a low mortality rate of 4 per cent was recorded[52]. The source of infection in this series was mainly the skin. Gangrene originating from anorectal sources has the highest associated mortality rate of the three major sources of sepsis[11,39,58,60].

Prognosis

Early aggressive treatment is associated with a reduced mortality rate[39,59,76,97]. Surprisingly, diabetes[16,42,60] and acquired immune deficiency syndrome[73,74] have been reported to have no adverse effect on survival in the disease, although some reports have associated age, diabetes mellitus, delay in treatment, alcoholism and colostomy with a poor prognosis[1,59,62,117]. Although antimicrobial agents are believed to be essential in the treatment of Fournier's gangrene, a few reports have indicated that the reduction in mortality rate is not attributable to the use of such agents[36,39,43].

Laor *et al.*[37] designed a Fournier's gangrene severity index along the lines of the Acute Physiology And Chronic Health Evaluation score in an effort to identify prognostic factors. They concluded, as found earlier by others[11,118], that deviation from homoeostasis was associated with a worse prognosis. Studies on the extent of body involvement with regard to mortality have produced conflicting results. Some authors have found no linear relationship, corroborating the findings of Clayton *et al.*[43] (but still concluded that patients with more than 5 per cent body-surface involvement in Fournier's gangrene were more likely to die[119]). However, others have found that local involvement was associated with a reduced mortality rate, compared with extensive body involvement[16,53].

Discussion

The controversy over the terminology of Fournier's gangrene is probably unnecessary, as there appears to be no significant fundamental difference in the proffered definitions. The specific pathological process, necrotizing fasciitis, in the specific region of the perineum and genitalia, should be termed Fournier's gangrene, the aetiology with or without proven infection notwithstanding. As Elliott *et al.*[120] have noted, 'distinguishing between the various categories of necrotizing soft tissue infections serves little purpose because the prognosis and treatment are the same'.

It is tempting to suggest that poor socioeconomic class is associated with Fournier's gangrene, but the geographical distribution that affects Europe and North America suggests that the disease is not restricted to the poor. The fundamental problem may be reduced immunity. The high incidence of the disease in the USA (*Fig. 2*) may also reflect the better opportunities for research and publications in that country.

The source of sepsis may be hidden. The local skin probably accounts for those cases in which haematogenous spread of infection has been postulated and for those where a source of infection is not apparent. It has been emphasized that the skin should be considered the source of infection when urological and coloanorectal sources have been excluded[60]. Any lesion originating in the skin is probably incorporated and consumed in the disease process. It is invariably excised in the surgical debridement of necrotic fascia, a case of throwing away the bad baby with the 'dirty dishwater'. Debridement is often carried out as an emergency before embarking upon diagnostic procedures.

Certain systemic conditions are sufficiently frequently encountered in association with Fournier's gangrene to suggest a causal rather than a casual relationship. Diabetes mellitus has been so frequently mentioned as an associate in the aetiology of all forms of necrotizing fasciitis, including Fournier's gangrene, that it is time to accord it a full status in the aetiology of this dreadful disease. The significance of this frequency is underscored when juxtaposed against the recognition accorded the frequency of the three anatomical sites from where sepsis may originate (*Table 1*). Diabetes mellitus is implicated in 20 per cent of cases while urological lesions are found in 19 per cent.

The multiplicity of organisms isolated from a case of Fournier's gangrene suggests that none of them can properly be regarded as the cause of the disease. These organisms are commensals below the pelvic diaphragm[11,16,95] and so they are opportunistic in addition to their synergistic activity. It is quite possible that there has been a failure to identify organisms in the dry penile gangrene found in diabetics in end-stage chronic renal failure. It is also possible that, in classical cases of Fournier's gangrene with proven bacterial presence, such infection is a secondary complication of a primary ischaemic process. Therefore ischaemia and infection may be akin to the chicken and the egg. Furthermore, even where bacterial involvement is evident, proof that this is the root cause may be lacking[38].

Although the aetiology, extent and complications of Fournier's gangrene may indicate radiological, endoscopic and laboratory investigations, its diagnosis is a clinical matter. The application of investigations such as ultrasonography, skin biopsy, computed tomography and magnetic resonance imaging in the primary diagnosis of the disease is esoteric.

The disparity in the number of male and female cases reported may be because the condition is under-recognized in females[39]. It is also possible that in adhering to Fournier's original description, limiting the disease to males, some clinicians do not recognize female genital necrotizing infections as Fournier's gangrene. Certainly there is no report of the disease (or of postpartum genital gangrene) in African females and many gynaecology textbooks do not mention the condition. While perineal necrotizing fasciitis was amply discussed in a recent gynaecology textbook, it was not termed Fournier's gangrene[121]. In the final analysis, it is likely that Fournier's gangrene is actually uncommon in females who have a better drainage of secretions in the perineal region (vaginally) than males. While this may account for fewer cases of genital necrotizing fasciitis in women, the relatively low incidence of Fournier's gangrene in children requires an alternative explanation, possibly the fact that many of the predisposing factors, such as diabetes, alcoholism and atherosclerosis, increase with ageing.

When Stephen *et al.*[39] reviewed Fournier's gangrene in their 1993 paper, there were 449 cases reported from 1979 to 1988 giving a mean of 45 cases per year. Since then, in 10 years from 1989 to 1998, about 973 cases have been reported in the English literature, giving a mean yearly incidence of 97 cases. Speculation about the cause of this rise includes increased awareness and reporting[39], and increasing longevity[1,38].

Treatment of Fournier's gangrene needs to be prompt, pragmatic and individualized (not stereotypic). Conservative treatment without surgery may suffice in some cases, but the remnant scrotum even in these may need 'coaxing to encase the testicular mass'[107]. Catheterization and colostomy are beneficial when indicated and when judiciously employed[38,59]. These procedures ought not be the subject of extreme opinion about their applicability (or otherwise).

The claims about the efficacy of honey require further consideration on the use of this substance. Perhaps difficulties in packaging and non-availability of unadulterated honey have contributed to the relatively light use of this natural material. However, honey, at best, can only be an adjunct to surgical treatment. Hyperbaric oxygen is also an adjunct in the treatment of Fournier's gangrene; the recommendation that the disease should be treated only in centres with facilities for hyperbaric oxygenation[122] is not, at present, a practical proposition, even if the technique were unequivocally accepted as beneficial. The facility is not generally available. Similarly, antimicrobial agents should be an adjunct to surgical elimination of the nidus of sepsis. In view of the usual polybacterial cultures, triple antimicrobial therapy is justified.

Surgical excision to rid the patient promptly of fetid necrotic tissue and rapid extension of gangrene, along with the treatment of predisposing conditions, is essential to achieve a cure[27–29,64,67,100]. The only tenable indication for orchidectomy is testicular gangrene[46,60,64]. Radical excision including healthy tissues, as advocated by some[10,78], should be avoided, as it is likely to sacrifice tissue needlessly[5,16,43,69]. It should, however, be appreciated that, as the pathological process is rapid and ongoing at the time of a debridement, identification of all critically ischaemic tissue at any single session of excision may be impossible. Finally, wound closure in the presence of sepsis flies in the face of prevailing surgical principles.

Conclusion

Fournier's gangrene is both a pathological diagnosis (necrotizing fasciitis) and a clinical condition (deep perineal sepsis). While there is a need to harmonize its definition, present controversies about definition do not impact significantly on the treatment of the disease. Such controversies are, therefore, probably diversionary. The diagnosis of Fournier's gangrene is clinical. The apparent lower incidence in women is partly due to under-reporting and partly to the better perineal drainage in that sex. Diabetes mellitus is so frequently associated with the disease as to merit full aetiological status. The basic treatment of Fournier's gangrene involves prompt extirpation of all non-viable tissue, limitation and abolition of any infective process present, and occasional anatomical reconstruction. All necrotizing fasciitis of the perineum, including the genitalia in both sexes and at all ages, regardless of the aetiology, with or without proven infection, should be brought under the umbrella of Fournier's gangrene.

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Digest

Professor Seiki Matsuno, Chief Editor of *Surgery Today* (*The Japanese Journal of Surgery*), has selected from the October to December 1999 issues of the journal for this quarter's digest. A digest of *BJS* for the same period written by Professor Pierre Guillou, Associate Editor, appears in the Japanese journal.

The digest for October to December 1999 covers several aspects of surgery: oesophagus, colon, rectum, liver, lung, cardiac surgery and general surgery.

Oesophagus

A study was conducted to evaluate lymph node metastasis as a key prognostic factor in oesophageal cancer[1]. Metastatic lesions in lymph nodes were grouped by histological morphology as intracapsular or extracapsular, and the significance of lymph node metastasis was evaluated by relating metastatic lesions to clinicopathological factors and patient prognosis. Forty-six of 81 patients who underwent resection of oesophageal cancer developed lymph node metastasis. These 46 patients were enrolled in a study analysing the relationship between the metastatic mode and clinicopathological factors. The frequency of extracapsular metastasis was significantly higher in patients with a great depth of cancer, three or more metastases, distant metastasis (n3 and n4), or severe lymphatic invasion. The prognosis was significantly worse in patients with extracapsular metastasis; this tendency was even noted in patients with three or more metastases, limited metastasis (n1 and n2), or mild lymphatic invasion (ly0 and ly1). These findings suggest that the metastatic mode reflects the degree of oesophageal cancer progression and is an important prognostic factor.

Colon and rectum

There were three reports on rectal cancer. Many studies have established the usefulness of serial monitoring of serum carcinoembryonic antigen (CEA) concentration for predicting recurrence and prognosis; however, few studies have so far investigated serum CEA-negative recurrence[2]. The aim of one study was to elucidate the nature of CEA-negative recurrence with respect to tumour angiogenesis. Fifty-seven patients with T_3/T_4 rectal cancer were divided into two groups according to serum CEA status. Angiogenesis was defined as the intratumoral vessel count by immunohistochemical staining using CD31. The CD31 count was significantly higher in patients with recurrence in both groups, and the ratio of nodal involvement was significantly higher in those with recurrence in the CEA-negative group. Local recurrence developed mainly in the CEA-negative group; however, the CD31 count predicted neither the sites of recurrence nor the relapse period in either group. A multivariate analysis showed a high CD31 count (greater than 26) to be a prognostic factor not only for recurrence but also for survival ($P = 0{\cdot}001$ and $P = 0{\cdot}04$ respectively). These results suggest that a high degree of tumour angiogenesis in sections of T_3/T_4 rectal cancer may be an important predictor for CEA-negative recurrence.

A second study aimed to determine the long-term effects of administering preoperative radiochemotherapy to patients with carcinoma of the lower rectum[3]. The outcome for 29 patients who underwent curative operation for carcinoma of the lower rectum after receiving radiochemotherapy in the form of 40·5 Gy accelerated hyperfractionation and a total dose of 3400 mg 5-fluorouracil given as suppositories, with or without hyperthermia, and for 48 patients who underwent surgery alone, were compared retrospectively. The tumours of all patients were diagnosed histologically as stage T_3. The cumulative 5-year survival rate and 5-year local recurrence-free rate of patients treated with radiochemotherapy plus surgery were significantly better than those of patients treated by operation alone, the respective values being 80 *versus* 60 per cent ($P = 0{\cdot}03$) and 96 *versus* 61 per cent ($P = 0{\cdot}004$). Dehiscence of the perineal wound, anastomotic leakage and postoperative ileus occurred at a similar frequency in both groups; however, perineal wound healing after abdominoperineal resection was delayed in patients treated with radiochemotherapy and surgery (42·7 *versus* 25·4 days; $P = 0{\cdot}006$). In conclusion, although wound healing was delayed, preoperative radiochemotherapy is considered to be beneficial for patients with carcinoma of the lower rectum.

Local recurrence is one of the major reasons that rectal cancer surgery is unsuccessful. The aim of a third study was to investigate the surgical characteristics of patients undergoing repeat resection for local recurrence of rectal cancer[4]. A total of nine patients was enrolled in this study, six of whom underwent total pelvic exenteration, one posterior exenteration, one abdominoperineal resection with sacral resection, and one lymph node dissection alone. The mean operating time was 8 h 15 min and the mean operative blood loss 2325 ml. Although major postoperative complications occurred in four patients, there were no postoperative or hospital deaths. Lateral lymph node metastasis was detected in all four patients whose lateral lymph nodes were dissected or extirpated at repeat resection. Two patients survived for more than 5 years without repeat recurrence and the cumulative 5-year survival rate was 26 per cent. The para-aortic lymph nodes were the most common site of first repeat recurrence. The results of this study indicate that patients who undergo repeat resection for local recurrence of rectal cancer are at high risk of developing lateral or para-aortic nodal metastasis. Nevertheless, repeat resection may be a therapeutic option for the local recurrence of rectal cancer.

The functional outcome after low anterior resection for rectal cancer is improved by a colonic J pouch reconstruction[5]. One functional problem with J pouches is difficulty in evacuation, which is more common with large reconstructions. Since rectoceles are common findings on defaecography in patients with evacuation difficulties, it has been proposed that a rectocele-like prolapse may be found in patients with large J pouches. Pouchography was used to identify a rectocele-like prolapse in 26 patients with a 10-cm J pouch and in 27 with a 5-cm J pouch. Pouchography was performed at 3 months, 1 year and 2 years after operation. Functional assessments were performed 1 year after operation. Clinical function was evaluated by means of a questionnaire. The evacuation function was evaluated by the balloon expulsion and saline evacuation test. No patient had a rectocele-like prolapse at 3 months or 1 year after operation. Two years after operation, a prolapse was significantly more common in patients in the 10-cm J pouch group than in those in the 5-cm group ($P = 0{\cdot}04$). An evacuation difficulty was significantly more common in the 10-cm than in the 5-cm J pouch group. The evacuation function in the 10-cm group was also significantly inferior to that in the 5-cm group. A rectocele-like prolapse appearing 2 years after operation is more common in patients with evacuation difficulties and large colonic J pouch reconstructions.

Liver

The objective of this study was to evaluate the significance of performing hepatectomy for primary intrahepatic stones[6]. Observations on the morphology of the bile ducts, histopathological findings of the excised liver and treatment results were reviewed in 29 of 35 patients with primary intrahepatic stones. The remaining six patients were excluded because they had intrahepatic cholangiocarcinoma. The subjects were classified into two groups according to the morphological characteristics of the bile ducts. One group comprised 25 patients with strictures in the central bile duct and the other group comprised four patients with no biliary strictures but a localized dilatation in the distal bile duct. Calcium bilirubinate stones were found in all patients with a biliary stricture, whereas cholesterol stones were found in those without a biliary stricture. Hepatectomy was performed in 25 of the 29 patients, the results of which were excellent. During the past 10 years, no postoperative complications have occurred, nor have there been any retained or recurrent stones. Moreover, the postoperative length of hospital stay was as short as 15·3 days. The findings of this study indicate that hepatectomy allows treatment for primary intrahepatic stones to be completed within a short period of time without incurring serious postoperative complications, and serves as a useful prophylactic technique for recurrent stones.

Hepatic phosphatidylcholine hydroperoxide (PCOOH) was studied intensively to delineate its role in the altered pathophysiology of liver failure associated with endotoxaemic shock[7]. Endotoxaemia was induced by caecal ligation and puncture (CLP) in three models using rats. Model 1 consisted of normal healthy rats; model 2 comprised cirrhotic rats; and in model 3 rats were treated with catalase and superoxide dismutase. Samples were taken before CLP, then 12 and 24 h after CLP. A progressive and significant increase in serum endotoxin concentration was noted in all models, but a significantly lower energy charge and high PCOOH level were noted in models 1 and 2, while no change was observed in model 3. The regional blood flow remained unchanged throughout the experiment in models 1 and 3, but not in model 2. An initial increase in α-tocopherol was found in model 1. The survival rate was markedly better in model 3 than in models 1 or 2. The fall in energy charge corresponded to the increase in serum endotoxin concentration as well as to the increase in tissue PCOOH levels in models 1 and 2. It was more likely that the increased lipid peroxidation in model 1 resulted from endotoxaemia rather than tissue hypoperfusion. The early increase in α-tocopherol concentration that occurred in models 1 and 2, but not in model 3, indicated the antiradical defence response to oxidative injury. Thus, antioxidant therapy significantly improved the survival rate and tissue adenine nucleotide concentration in spite of the increased serum endotoxin level.

Hepatic ischaemia was induced by clamping the hepatic artery, portal vein and bile duct[8]. After 15 min ischaemia, the hepatic glutathione (GSH) content rapidly decreased. On the other hand, after the start of reperfusion hepatic GSH levels increased promptly and reached a peak at about 1 h, and thereafter decreased to a minimum level by 2 h. Under such conditions, the changes in methionine adenosyltransferase (MAT) activity were examined in the liver. Although the time course of MAT activity was somewhat delayed compared with that of hepatic GSH levels, both patterns were substantially similar during ischaemia–reperfusion. In contrast to the changes in MAT activity during ischaemia–reperfusion, the levels of MAT protein were unchanged during these periods. When endogenous antioxidant coenzyme Q10 (CoQ10) was administered to rats before ischaemia, both the reduction in MAT activity and hepatic GSH levels induced by ischaemia–reperfusion were protected. These findings suggest that CoQ10 may regulate the MAT activity post-translationally via the changes in GSH level in the liver.

A study was carried out to examine the protective effects of guanosine 3′, 5′-cyclic monophosphate (cGMP), a second messenger of nitric oxide, for ischaemia–reperfusion injury of the liver, as cGMP is known to induce vasodilatation and inhibit platelet aggregation[9]. Using an experimental model of porcine liver ischaemia, 8-bromoguanosine 3′,5′-monophosphate, a cGMP analogue, was administered continuously into the portal vein before ischaemia and for 30 min after reperfusion for each animal in the cGMP group ($n = 6$). Saline was administered in the same way in the control group ($n = 6$). The cardiac output, mean arterial blood pressure (MAP), portal venous flow (PVF), hepatic arterial flow (HAF), hepatic tissue blood flow (HTBF) and hepatic tissue cGMP concentration were determined. Hepatic enzymes and bile discharge were also assessed as indicators of hepatic function. The hepatic tissue cGMP level was significantly higher, and PVF, HTBF and bile discharge were significantly greater in the cGMP group, while there were no remarkable differences between the groups with respect to cardiac output, MAP, HAF and hepatic enzymes. In conclusion, the continuous supplementation of cGMP into the portal vein was found to be beneficial for preserving both the hepatic circulation and, consequently, hepatic function after warm ischaemia of porcine liver.

Lung

The effects on pulmonary function of circulating inflammatory cytokines and adhesion molecules induced by orthotopic liver transplantation were investigated[10]. Although the plasma interleukin (IL) 8 level increased gradually, peaking at the end of the operation, these increases were considered minimal. The baseline level of endothelial adhesion molecule (E-selectin) was several times higher than the normal value but, after reperfusion of the new transplanted liver, plasma E-selectin concentration decreased to within the normal range and remained almost normal during the postoperative period. Similar changes were observed in the plasma levels of other types of adhesion molecules. Although the ratio of arterial partial pressure of oxygen ($P\mathrm{aO_2}$)/fraction of inspired oxygen ($F\mathrm{IO_2}$) showed a significant inverse correlation with the peak IL-8 concentration, after the exclusion of two patients (one of whom died and one of whom rejected the transplanted liver) no correlation was found between the $P\mathrm{aO_2}/F\mathrm{IO_2}$ ratio and the maximum IL-8 concentration. Furthermore, there was no correlation between the adhesion molecules and $P\mathrm{aO_2}/F\mathrm{IO_2}$. These results suggest that IL-8 exerts only a slight effect on respiratory function following successful paediatric liver transplantation and that circulating adhesion molecules do not affect perioperative lung function.

The aim of another study was to evaluate the relationship between polymorphonuclear elastase (PMNE) and urinary trypsin inhibitor (UTI) concentrations in the bronchoalveolar lavage fluid of patients with adult respiratory distress syndrome (ARDS)[11]. Eight patients who developed ARDS after gastroenterological surgery and eight patients with normal respiratory function during general anaesthesia using tracheal intubation were the subjects of the study. Lavage fluid was collected from the right middle lobe using saline, and PMNE and UTI concentrations were measured. The mean(s.d.) PMNE concentration was 1277(1589) and 38(26) ng/ml in patients with ARDS and normal lung function respectively, and the UTI concentration was 225(175) and 81(40) munits/ml respectively. Based on the UTI concentration that can inhibit PMNE activity, the PMNE concentration in patients with ARDS was not inhibited entirely by UTI. Since only UTI can inhibit PMNE activity in inflammatory tissues, PMNE in the lavage fluid may induce and aggravate lung injury in ARDS. Thus, the authors conclude that PMNE released from activated neutrophils in the lung is associated with the development of ARDS.

A study was conducted to investigate the role of nitric oxide in the development of ARDS[12]. An experimental model of endotoxaemia-induced ARDS was prepared in guinea-pigs and the following variables were measured: pulmonary vascular permeability, the nitrate and nitrite concentrations in blood and bronchoalveolar lavage fluid, and the activities of constitutive and inducible nitric oxide synthase in lung tissue following the administration of lipopolysaccharide (LPS). After intravenous administration of LPS 0·5 mg/kg, pulmonary vascular permeability increased, as did the concentration of nitrate and nitrite in the lavage fluid blood. The activities of both constitutive and inducible nitric oxide synthase increased significantly in the lung tissue 4 h after the intravenous administration of LPS, the constitutive form showing significantly higher activity than the inducible form. Furthermore, the increase of vascular permeability in the lungs after LPS injection was blocked by the subcutaneous administration of N^{G}-monomethyl-L-arginine. These observations indicate that the intrapulmonary generation of nitric oxide may play an important role in the development of ARDS.

The purpose of another study was to clarify which factors were important as predictors of both patient survival and haematogenic metastasis in 15 patients with stage I lung adenocarcinoma who underwent curative operation[13]. The relationship between tumour angiogenesis, apoptosis and *p53* oncogene was also studied. A total of 15 patients was divided into two groups: surviving group ($n = 7$) and non-surviving (metastasis) group ($n = 8$). The medical charts, operative records, pathological reports and tumour specimens taken at surgical resection were studied. The apoptotic index, using the ApopTag kit, and the intratumoral microvessel count, using an anti-CD34 monoclonal antibody, were measured. In addition, immunohistochemical staining for the expression of p53 was conducted simultaneously. The clinicopathological characteristics, including age, sex, tumour size (pathological tumour status; pT) and histological differentiation, were not significantly different between the surviving and non-surviving groups. The microvessel count was significantly higher in the non-surviving than in the surviving group. The apoptotic index and the expression of p53 were not significantly different between the two groups. An inverse correlation between the apoptotic index and microvessel count, and a positive correlation between the expression of p53 and microvessel count, were observed. Angiogenesis may be an important prognostic factor in patients with stage I lung adenocarcinoma.

Cardiac surgery

The authors of this study defined injuries to the heart and the pericardium together with haemopericardium as pericardial tamponade-type injury regardless of symptoms or signs due to pericardial tamponade[14]. The aim of the study was to examine the important factors related to the diagnosis and treatment of this type of injury. A retrospective chart review was conducted of traumatized patients admitted with haemopericardium between 1978 and 1995. Ten of 19 consecutive patients with pericardial tamponade-type injury demonstrated shock and showed a higher Injury Severity Score and mortality rate than the remaining nine without shock. The majority of the patients received an emergency thoracotomy or a surgical fenestration in the accident and emergency department, and thereafter some needed a (re-)thoracotomy in the operating room. The authors concluded that a fenestration through the pericardium is the first choice for the relief of acute haemopericardium due to trauma; surgeons should not perform pericardiocentesis for either the diagnosis or relief of this type of injury.

Two important unsolved questions relating to peripheral parenteral nutrition involve the ratio of components in the intravenous solution and catheter-related complications. A study was undertaken to evaluate the nutritional profiles of three kinds of intravenous solutions with different ratios of components, while maintaining the total energy at about 1200 kcal/day and the amino acid level at 60 g. The intravenous solution formulas used were as follows: glucose : fat ratio of 2 : 1, osmolarity ratio 3·3 for group A; glucose : fat ratio of 1 : 1, osmolarity ratio 3·1 for group B; and glucose : fat ratio of 1 : 2, osmolarity ratio 2·6 for group C. The incidence and severity of complications were then analysed in relation to the type of intravenous solution used, the indwelling catheter time, and the type of catheter (midline catheter or short peripheral catheter). The results of peripheral parenteral nutrition were favourable when the glucose : fat ratio of the intravenous solution was either 1 : 1 or 1 : 2[15]. The midline catheter was inserted for an average of 11·9 days, and the incidence of catheter-related complications following parenteral nutrition with a midline catheter was low when the osmolarity ratio of the intravenous solution was 3·1 or less. These results indicate that a midline catheter is useful when administering peripheral parenteral nutrition.

General surgery

Pancreatic tissue concentrations of cefazolin were examined in ten patients undergoing pancreatectomy and the optimal intraoperative time to deliver a repeat dose of cefazolin was determined[16]. An intravenous bolus dose of cefazolin 1 g was administered at the time of skin incision. Peripheral blood, subcutaneous adipose tissue and peritoneal samples were obtained during operation every hour for 4 h after the antibiotic was first administered, and pancreatic tissue samples were obtained at the time of pancreatectomy. To determine adequate tissue levels of cefazolin, the minimum inhibitory concentration (MIC) was measured for four bacterial species, namely 360 isolates of methicillin-sensitive *Staphylococcus aureus*, 204 isolates of *Klebsiella pneumoniae*, 314 isolates of *Escherichia coli* and 30 isolates of *Streptococcus* spp. Antibiotic concentrations in adipose tissue and peritoneum 3 h after the administration of cefazolin were lower than the MIC_{80} for *K. pneumoniae*, *E. coli* and *Streptococcus* spp. Most pancreatic tissue samples showed antibiotic concentrations greater than the MIC_{80} for these bacterial species; however, those from four patients with complications of severe chronic pancreatitis, massive intraoperative bleeding or obesity showed concentrations lower than the MIC_{80}. The authors concluded that a second dose of cefazolin should be given 3 h after the first to maintain adequate levels of antibiotics.

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Vascular Surgical Society of Great Britain and Ireland

The annual scientific meeting of the Vascular Surgical Society of Great Britain and Ireland was held in Leicester on 24–26 November 1999 under the Presidency of Professor P. R. F. Bell. Abstracts of the presentations given at the meeting were published in the April issue of the BJS. The following articles are based on presentations from the Leicester meeting and were accepted for publication after peer review by the Journal's referees. Other papers from the meeting will appear in future issues.

Jonothan Earnshaw
Associate Editor

Vascular Surgical Society

Reperfusion injury is greater with delayed restoration of venous outflow in concurrent arterial and venous limb injury

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Background: Complex limb trauma often involves combined arterial and venous injury, and the resultant ischaemia–reperfusion injury (IRI) causes both local and remote organ injury. This study assessed the influence of the timing of restoration of venous drainage on IRI.

Methods: Male New Zealand white rabbits ($n = 36$) were randomized into six groups: sham operation (group 1) and unilateral hind limb arterial and venous occlusion for 1 h followed by no reflow for 2 h (group 2), arterial and venous reflow for 2 h (group 3), arterial reflow alone for 2 h (group 4), arterial reflow alone for 1 h followed by arterial and venous (delayed) reflow for a further 1 h (group 5), and pretreatment with an enteral combination antioxidant before occlusion of both artery and vein and delayed venous reflow (group 6). Plasma hydroperoxide (HPO) and glutathione peroxidase concentration, hind limb skeletal muscle and lung tissue wet : dry weight ratios and myeloperoxidase (MPO) concentration were measured.

Results: The plasma HPO level in the femoral vein effluent was significantly greater after delayed venous reflow (mean(s.e.m.) 2·02(0·54) μmol/l) than in control animals (0·98(0·10) μmol/l) ($P < 0·05$). There was also a significantly greater tissue wet : dry weight ratio after delayed venous reflow than in controls, in skeletal muscle (mean(s.e.m.) 6·89(0·14) *versus* 5·34(0·54); $P < 0·05$) and lung (9·20(1·14) *versus* 7·23(0·38); $P < 0·05$) tissue. Lung tissue MPO activity was significantly greater after delayed venous reflow compared with controls (3·20(0·28) *versus* 1·86(0·14) units/g; $P < 0·005$), and also in comparison to simultaneous arterial and venous reflow (2·40(0·24) units/g; $P < 0·05$). In the antioxidant pretreatment group there was no significant increase in plasma HPO concentration, tissue MPO level

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British Journal of Surgery Prize winning paper at the annual meeting of the Vascular Surgical Society of Great Britain and Ireland, Leicester, UK, November 1999. Presented in part to the Surgical Research Society, Brighton, UK, May 1999 and the European Society for Surgical Research, Bern, Switzerland, 1999; and published in abstract form as *Br J Surg* 1999; 86(Suppl 1): 24

or tissue wet : dry weight ratio compared with the control group.

Conclusion: In combined major arterial and venous injury of the limb, delayed restoration of venous drainage leads to significantly greater local skeletal muscle injury and remote neutrophil-mediated lung injury. These results support the clinical rationale for early restoration not only of arterial inflow but also venous drainage by means of intraluminal shunts.

Paper accepted 26 February 2000

British Journal of Surgery 2000, 87, 734–741

Introduction

Major limb trauma is an important cause of disability in some of the most productive members of society[1]. Half of these complex injuries involve combined arterial and venous injury, often featuring transection, avulsion or crushing of long vessel segments and frequently accompanied by varying degrees of osseous, neurological and soft tissue trauma as well as contamination of the wounds[1–8].

The recorded limb amputation rate for such injuries is as high as 85 per cent[4–7]. Control of bleeding, resuscitation and definitive revascularization surgery, even when achieved expeditiously, requires a finite and sometimes unacceptably prolonged interval, especially in patients who have suffered multiple injuries. Striated muscle does not tolerate ischaemia exceeding 6–8 h. Such time constraints and an understandable desire to restore flow quickly may induce lapses of surgical principle or of operative technique in terms of quality of vascular repair, wound care and bone fixation. The priority given to restoring arterial inflow is often at the expense of delayed repair or ligation of the main venous channel. The resulting acute venous and compartment hypertension impairs tissue perfusion, may compromise the arterial repair and diminish the chance of limb salvage[3].

For the past two decades the policy at this centre has been for early intraluminal vascular shunting of both artery and vein in order simultaneously to arrest ischaemia, restore venous drainage, permit optimal wound care and allow bone stabilization before repair of both artery and vein[9–16]. This experience of shunting has imposed a logical operative approach that dispels anxieties about time and assures clinical dividends by way of lower fasciotomy rates, reduced incidence of sepsis and better limb salvage[16].

In situations where arterial flow is temporarily interrupted, the pathophysiology of the local and distant reperfusion-induced injury has been characterized[17–23]. However, the manner in which these consequences might be influenced by concomitant venous injury remains to be elucidated. In limb trauma involving combined major artery and vein injury, acute impairment of venous drainage and venous congestion leads to increased peripheral resistance and decreased arterial inflow, compounding existing tissue hypoxia. Pure arterial ischaemia–reperfusion injury (IRI) of the limb has been shown to initiate a systemic inflammatory response syndrome associated with multiple organ dysfunction syndrome and death[22,23]. If this sequence occurs in combined artery and vein injury the time taken to re-establish venous reflow in relation to arterial reperfusion may be a crucial factor in the development of local and distant IRI.

Oxygen reactive species created by reperfusion initiate local skeletal muscle injury and subsequent neutrophil activation and degranulation. This process not only compounds local injury but promotes remote acute lung damage[24–26]. Failure of local antioxidant scavenging systems in the face of the overwhelming production of oxidants is central to the injury associated with oxidative stress[27]. Although a variety of exogenous antioxidant supplements have been shown to attenuate reperfusion injury, especially if administered before the ischaemic insult[27], their potential benefit in combined major arterial and venous injury of the limb has not been studied.

In an animal model of hind limb major injury the present study investigated the effects of temporary combined vessel occlusion on local skeletal muscle and distant lung injury. Further, the effect of simultaneous, delayed or non-reflow of the vein on outcome was explored, and the effects of using antioxidant pretreatment on that outcome were examined.

Materials and methods

Thirty-six adult male New Zealand white rabbits weighing 2·5–3·5 kg were anaesthetized with hypnorm (fentanyl citrate 0·315 mg/ml and fluanisone 10 mg/ml) 0·3 ml/kg intramuscularly and midazolam 1 mg/kg intravenously (Janssen Pharmacutica, Beerse, Belgium). A heparinized cannula was inserted in the left marginal ear vein and normal saline was infused at 10 ml per kg per h; animals were given heparin 500 units/kg intravenously. Temperature was monitored with a rectal temperature probe and maintained at 38 ± 1·0°C by use of a heating blanket.

Anaesthetized animals underwent a right groin dissection with isolation of the right common femoral artery and vein; all collateral vessels in the anterior thigh were ligated *in situ* at this level. After systemic heparinization (heparin 500 units/kg), right common femoral artery and vein occlusion was induced by application of vascular bulldog arterial clamps. In control animals the right common femoral vessels were exposed but not clamped. Absence of flow, and restoration (by clamp release) if appropriate, was confirmed using an ultrasonic flow probe (Transonic Systems, Ithaca, NY, USA) applied to the vessel wall.

The experimental aim was to investigate the effect of combined arterial and venous occlusion–reperfusion on local limb and distant lung injury, and to explore the effect of the timing of restoration of venous drainage on these outcomes. Animals ($n = 30$) were randomized into five groups (*Fig. 1*). Controls (group 1) underwent sham operation and the other four groups had 1 h of unilateral hind limb arterial and venous occlusion followed by no reflow for 2 h (group 2), arterial and venous reflow for 2 h (group 3), arterial reflow alone for 2 h (group 4), and arterial reflow alone for 1 h followed by arterial and venous (delayed) reflow for a further hour (group 5).

A further group of six animal (group 6) was pretreated, by gavage, three times daily for 2 weeks with an enteral combination antioxidant preparation, Quantox (Pharma Nord, Morpeth, UK), before undergoing combined vessel occlusion for 1 h followed by arterial reflow alone for 1 h then arterial and venous (delayed) reflow for a further hour.

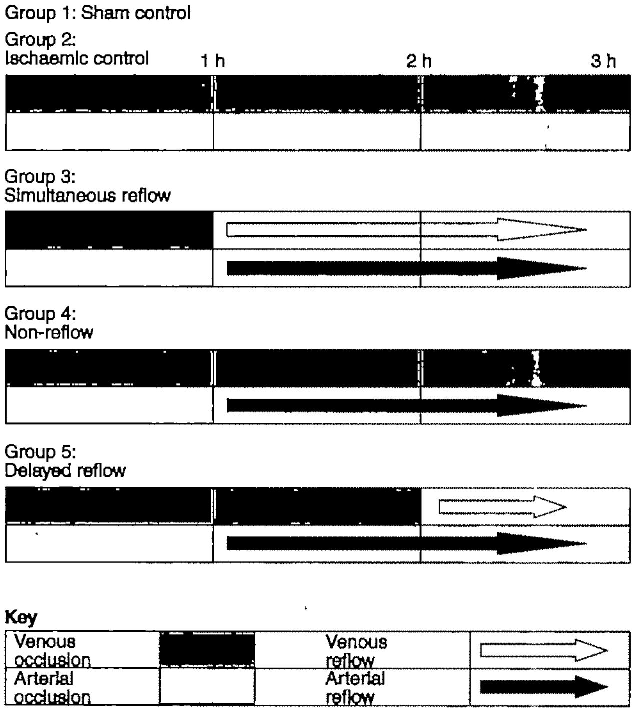

Fig. 1 Schematic representation of the sequence of arterial and venous occlusion and reflow in experimental groups 1–5. All interventions refer to the right common femoral vessels

Blood was withdrawn from the right ear vein before any vessel occlusion and then every 30 min during the ischaemia and reperfusion interval. A blood sample was withdrawn from the right common femoral vein after reperfusion, then the rabbit was killed with an overdose of sodium pentobarbitol. At termination of the experiment skeletal muscle tissue from the right anterior thigh and right lung tissue were harvested, snap frozen in liquid nitrogen and stored at −70°C until analysed.

Measurement of myeloperoxidase activity

To determine myeloperoxidase (MPO) activity in tissue, the specimen (200–400 mg) was minced in a beaker containing 1 ml Hexa-decyltrimethylammonium bromide (HTAB) buffer on ice, transferred to a test tube and homogenized with a Polytron (CAMLAB, Cambridge, UK) homogenizer (three times for 30 s each, on ice). After homogenization the homogenizer was rinsed twice with 1 ml HTAB. The pooled homogenate and washes were sonicated for 10 s, freeze–thawed three times and centrifuged at 40 000*g* for 15 min. The supernatant was assayed for MPO activity. MPO activity was measured spectrophotometrically: 0·1 ml supernatant was combined with 2·9 ml phosphate buffer 50 mmol/l pH 6·0, containing O-dianisidine hydrochloride 0·167 mg/ml and 0·0005 per cent hydrogen peroxide. The change in absorbance at 460 nm was measured with a Beckmann DU-2 spectrophotometer (Beckmann Instruments, Cedar Grove, New Jersey, USA). One unit of MPO activity was defined as that degrading 1 μmol of peroxide per min at 25°C.

Measurement of serum hydroperoxide levels

Serum hydroperoxide (HPO) levels were measured spectrophotometrically by the FOX method 1 (ferrous oxidation in xylenol orange)[28]. The recipe for the sorbitol-containing version of the water-soluble HPO assay, referred to as FOX1, contained xylenol orange 100 μmol/l (water soluble form; Sigma, St Louis, Missouri, USA or Aldrich, Milwaukee, Wisconsin, USA), ammonium ferrous sulphate 250 μmol/l, sorbitol 100 μmol/l and sulphuric acid 25 μmol/l. In short, 50 μl of the serum sample was added to 950 μl FOX1 reagent (in a 1-ml microcentrifuge vial), vortexed and incubated at room temperature for a minimum of 30 min, at which time colour development was virtually complete. The absorbance was read at 560 nm after removal of any flocculated material by centrifugation. The signal was read against a hydrogen peroxide standard curve which was linear in the 0–5-µmol/l concentration range. Coefficients of variation were less than 3 per cent.

Measurement of serum glutathione peroxidase levels

Serum glutathione peroxidase (GSHPx) was estimated using the Cobas Fara centrifugal analyser (Roche Products, Welwyn Garden City, UK), by a method described by McMaster *et al.*[29]. GSHPx catalyses the oxidation of reduced glutathione (GSH) by hydrogen peroxide. The substrate is maintained at a constant concentration by the addition of glutathione reductase (GSSG-R) and reduced nicotinamide adenine dinucleotide phosphate (NADPH). The decrease in absorbance of the reaction mixture at 340 nm is a measure of GSSG production. In short, clotted blood was centrifuged (1500*g*, 4°C, 10 min); the supernatant was transferred to a clean plastic tube and recentrifuged under the same conditions to yield clear serum. GSH, NADPH and GSSG-R were all obtained from BCL (Lewes, UK), hydrogen peroxide was from Hopkins and Williams (Chadwell Heath, UK) and all other chemicals were from BDH Chemicals, Belfast, UK. The stock buffer contained potassium phosphate 10·2 g/l, 30·0 ml/l of disodium ethylenediamine tetra-acetic acid 0·1 mol/l and sodium azide 0·4 mg/l. The pH was brought to 7·0 with a solution of sodium hydroxide 1 mol/l. The principal reagent contained 3·5 mg NADPH, 10 mg GSH, 6 units GSSG-R and 500 µl Drabkin's reagent in 8·67 ml of buffer. The start reagent consisted of 50 µl hydrogen peroxide 9·8 mol/l (confirmed by titration) in 100 ml distilled water. The reagents were prepared immediately before use and kept at 4°C in an ice bath. A 200-µl sample of supernatant was added to an analyser cup and the enzyme activity was assayed automatically by the computer-controlled instrument. The system was operated by software version 23–3507. With the test program used the sample, dilutant and the principal reagent were pipetted simultaneously into the analyser rotor and mixed. A blank, consisting of reagent and dilutant, was included automatically. After incubation for 60 s at 37°C, start reagent (hydrogen peroxide) was added to the cuvettes. After acceleration and mixing, the absorbance was read at the preprogrammed time intervals. All calculations were done by the computer and were based on the change in absorbance between reading 7 and 13, i.e. after 70 s of equilibration and reaction. Various checks were made on the data and, if the reaction was satisfactory, linear regression was performed on the absorbance points within the specified interval. The rate of change for each sample, enzyme activity, was reported as units per litre of serum.

Histological examination

Tissue samples were fixed in 10 per cent formaldehyde and embedded in paraffin, and 5-µm thick sections were cut. Tissue samples were stained with haematoxylin and eosin. Polymorphonuclear leucocytes (neutrophils) were identified by standard morphological characteristics, and were counted in 50 high-power fields using a Nikon Labophoto microscope (Nikon, Instrument Group) by an experienced pathologist blinded to the sample groups.

Tissue wet : dry weight ratios

Wet : dry ratios were obtained on lung and skeletal muscle tissue samples (200–400 mg). Each specimen was blotted dry, weighed then placed in a vacuum freeze-dryer at −70°C for 48 h. Specimens were then reweighed and the wet : dry tissue weight ratio was calculated.

Statistical analysis

Data are presented mean(s.e.m.). Differences among groups were evaluated by one-way analysis of variance with Student's *t* test for between-group comparisons. Differences were considered significant when $P < 0·05$.

Results

Plasma hydroperoxide levels (*Table 1*)

There was no significant difference in plasma HPO concentration between the control group and groups with 1 h of arterial and venous occlusion followed by no reflow, arterial reflow alone or simultaneous arterial and venous reflow. Plasma HPO level in the femoral vein effluent was significantly greater ($P < 0·05$) in the delayed venous reflow group (2·02(0·54) µmol/l) compared with that in control animals (0·98(0·10) µmol/l). In the group pretreated with antioxidant vitamins and subjected to delayed venous reflow there was no significant increase in plasma hydroperoxide concentration.

Serum glutathione peroxidase levels (*Table 2*)

GSHPx levels were significantly greater in the antioxidant pretreatment group compared with controls in the systemic circulation before ischaemia (607·85(36·27) *versus* 414·85(31·67) units/l; $P < 0·003$) and at the end of the experiment (562·29(40·65) *versus* 391·35(33·41) units/l; $P < 0·009$). Serum GSHPx levels in the systemic circulation were significantly greater before the ischaemia

Table 1 Plasma hydroperoxide concentration in systemic vein before and after intervention, and in the femoral vein effluent after intervention

	Plasma hydroperoxide (µmol/l)		
	Systemic vein		Femoral vein
Group	Start	Endpoint	Endpoint
1 Control	0·92(0·19)	1·26(0·25)	0·98(0·10)
2 Ischaemic control	1·06(0·18)	1·06(0·25)	1·77(0·53)
3 Simultaneous reflow	1·14(0·41)	1·32(0·52)	1·15(0·36)
4 Non-reflow	1·36(0·37)	0·87(0·14)	1·73(0·33)
5 Delayed reflow	1·22(0·14)	1·45(0·38)	2·02(0·54)*
6 Delayed reflow, antioxidant pretreatment	0·91(0·21)	1·30(0·30)	1·30(0·30)

Values are mean(s.e.m.). *$P < 0·05$ versus control group. One-way ANOVA and Student's *t* test.

Table 2 Serum glutathione peroxidase concentration in systemic vein before and after intervention, and in the femoral vein effluent after intervention

	Serum glutathione peroxidase (units/l)		
	Systemic vein		Femoral vein
Group	Start	Endpoint	Endpoint
1 Control	414·85(31·67)	391·35(33·41)	440·11(47·24)
2 Ischaemic control	488·60(45·60)	363·20(62·40)	291·70(10·90)
3 Simultaneous reflow	423·10(68·30)	398·60(63·90)	409·10(63·90)
4 Non-reflow	408·80(26·40)	399·01(35·40)	397·33(26·40)*
5 Delayed reflow	468·01(40·80)	412·20(35·60)	358·40(22·00)
6 Delayed reflow, antioxidant pretreatment	607·85(36·27)†	562·29(40·65)†	547·19(24·86)‡

Values are mean(s.e.m.). *$P < 0·05$, †$P < 0·01$, ‡$P < 0·005$ *versus* control group. One-way ANOVA and Student's *t* test.

(607·85(36·27) *versus* 467·96(40·75) units/l; $P < 0·028$) and after delayed venous reflow (562·29(40·65) *versus* 412·20(35·60) units/l; $P < 0·020$) in the antioxidant pretreatment group compared with the group without such pretreatment. In the femoral vein effluent after delayed venous reflow, GSHPx levels remained significantly higher in the antioxidant pretreatment group compared with the no pretreatment group (547·19(24·86) *versus* 358·40(22·00) units/l; $P < 0·001$).

Tissue wet : dry tissue weight ratios (*Fig. 2*)

There was a significantly greater tissue wet : dry weight ratio in the delayed venous reflow group compared with control animals, in skeletal muscle (6·89(0·14) *versus* 5·34(0·54); $P < 0·05$) and lung (9·20(1·14) *versus* 7·23(0·38); $P < 0·05$) tissue. This increase was also highly significant in comparison to the simultaneous arterial and venous reflow group (group 3), in skeletal muscle (6·89(0·14) *versus* 4·94(0·28); $P < 0·01$) and lung (9·20(1·14) *versus* 5·01(0·76); $P < 0·01$) tissue. In the group pretreated with antioxidant vitamins and subjected to delayed venous reflow there was no significant increase in tissue wet : dry weight ratio compared with controls.

Tissue myeloperoxidase activity (*Fig. 3*)

Lung tissue MPO activity was significantly greater in the delayed venous reflow group (3·20(0·28) units/g) than in controls (1·86(0·14) units/g; $P < 0·005$) and group 3 (2·40(0·24) units/g; $P < 0·05$). In the group pretreated with antioxidant vitamins and subjected to delayed venous reflow

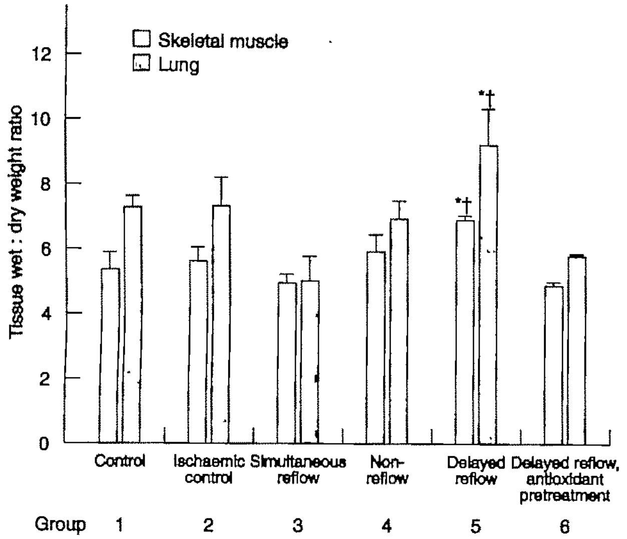

Fig. 2 Effect of timing of restoration of venous drainage on skeletal muscle and lung tissue oedema after temporary combined arterial and venous occlusion. Values are mean(s.e.m.). *$P < 0{\cdot}05$ *versus* control, †$P < 0{\cdot}01$ *versus* simultaneous reflow and antioxidant pretreatment. One-way ANOVA and Student's *t* test.

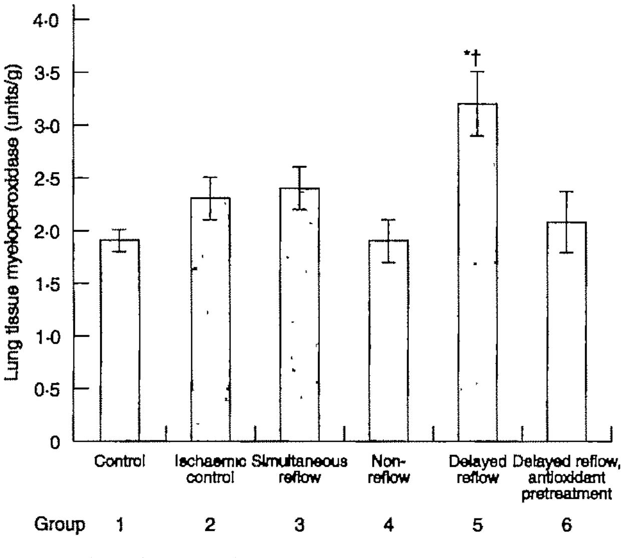

Fig. 3 Effect of timing of restoration of venous drainage on lung tissue leucosequestration after temporary combined arterial and venous occlusion. Lung tissue myeloperoxidase concentration is a measure of neutrophil infiltration. Values are mean(s.e.m.). *$P < 0{\cdot}005$ *versus* control group, †$P < 0{\cdot}05$ *versus* simultaneous reflow and antioxidant pretreatment. One-way ANOVA and Student's *t* test.

there was no significant increase in tissue MPO levels compared with controls.

Neutrophil counts

Lung tissue was examined at × 40 and neutrophils were counted in ten high-power fields. A significantly greater number of neutrophils was present after delayed venous reflow compared with controls and simultaneous arterial and venous reflow. The relationship between lung tissue neutrophil counts and lung tissue MPO levels showed a positive correlation between tissue MPO and mean neutrophil counts in ten high-power fields ($r = 0{\cdot}92$, $P < 0{\cdot}0002$).

Discussion

Complex limb trauma involves injury to a major artery and vein in up to 50 per cent of cases[1–8]. Crucial to limb survival is the timely restoration of arterial inflow, acknowledging the paradoxically harmful local and distant effects of IRI[22,23]. Concurrent venous damage may promote skeletal muscle injury by increasing venous congestion and oedema, impairing arterial reflow, and extending exposure of tissues to toxic metabolites such as lactate[8,21].

This study demonstrated that animals subjected to delayed venous drainage developed significantly more limb oedema, and lipid peroxidation as shown by the products of oxidative injury on reperfusion. It has also shown that in combined arterial and venous injury, temporary obstruction and delayed venous reflow was associated with remote lung oedema and neutrophil infiltration, consistent with the kind of acute lung injury observed after lower-torso IRI. Simultaneous restoration of venous outflow at the time of arterial reperfusion appeared to minimize both local as well as remote injury in this model. The group with no reflow of the vein also appeared to sustain less local and distant injury than the delayed venous reflow group. In the clinical situation, however, sustained occlusion of the common femoral vein inevitably leads to the harmful acute and chronic sequelae of venous hypertension.

Despite the relative resistance of skeletal muscle to ischaemic injury, Formigli *et al.*[30] found significant injury after as little as 45 min of ischaemia. Marked skeletal muscle oedema and evidence of membrane lipid peroxidation were noted in the delayed venous reflow group, effects that were reversed by antioxidant treatment. Certainly a longer ischaemic interval in the delayed reflow group could have produced more notable local injury had the already profound acute lung injury not proved lethal. Independent pathological assessment of skeletal muscle revealed a significantly increased pathological injury score in the delayed venous reflow group. Increased lung oedema (wet : dry weight ratio) and the presence of MPO in the lung, together with histological evidence of neutrophil infiltration and interstitial oedema, suggested that lung injury is neutrophil mediated in this model.

Quantox is an oral combination antioxidant treatment (containing selenium, methionine, beta-carotene, vitamin C, vitamin E and coenzyme Q10) shown to decrease injury due to oxidative stress in a range of clinical conditions[31,32]. The enzyme GSHPx catalyses the reduction of organic hydroperoxides, and thus is an important intracellular antioxidant. Its measurement in serum has been described as a reliable measure of antioxidant status[29]. Selenium and methionine supplementation has been shown to enhance the production of GSHPx. Levels of GSHPx can be enhanced by preloading with combination antioxidant supplements and levels of this important endogenous antioxidant remain significantly raised after temporary combined arterial and venous occlusion with delayed venous reflow. This may be protective against oxidative injury, as less lipid peroxidation, tissue oedema and neutrophil-mediated lung injury were observed in the group treated with Quantox in comparison to the group that did not receive such pretreatment. In the trauma situation the ischaemic period has already been initiated and therefore preloading is not of any value; Ytrehus *et al.*[33] have shown that even intravenous antioxidants are less beneficial once ischaemia has begun. Attempted modulation of neutrophil activation and degranulation has been shown to be protective in postischaemic tissue[24–26] and this may prove to be a more promising line of research. In the present study enteral preloading was used before the onset of ischaemia, to ensure improved local and global antioxidant levels.

Ample clinical experience at this centre, especially in complex limb vascular trauma, has demonstrated the value of early placement of intraluminal shunts in both artery and vein when both vessels are injured concomitantly[9–16]. This policy ensures both early restoration of arterial inflow, arresting ischaemia time, and simultaneous venous drainage preventing venous congestion. This allows time for meticulous wound care and debridement, attention to nerve injury, optimal skeletal fixation, and unhurried and appropriate arterial and venous repair[9–16]. The results of this experimental study lend support to the rationale that has governed the policy and practice of shunting at this vascular centre.

In conclusion, combined major arterial and venous injury of the lower limb with delayed venous reflow was associated with increased local skeletal muscle oedema and membrane lipid peroxidation and, in turn, neutrophil-mediated remote lung injury. The results suggest that reduction in local skeletal muscle and distant lung injury can be achieved by simultaneous restoration not only of arterial inflow but also of venous outflow. These experimental findings reaffirm the acknowledged clinical benefits of the early use of intraluminal shunts in both artery and vein in combined major vessel injury of the limb.

Acknowledgements

The authors are grateful to Dr B. Lister and Pharma Nord (UK) Ltd for the kind provision of Quantox. A grant from the Department of Health and Social Services Northern Ireland and The Royal Hospitals Research Trust is acknowledged.

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Risk factors for postoperative death following elective surgical repair of abdominal aortic aneurysm: results from the UK Small Aneurysm Trial

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Background: In regional and population studies, the mortality rate within 30 days of elective surgical repair of abdominal aortic aneurysm is approximately 8 per cent. Identification of preoperative factors associated with this mortality risk is important for informing surgical policy and may suggest suitable preoperative interventions.

Methods: In the UK Small Aneurysm Trial, 820 patients aged 60–80 years underwent elective open surgical repair of an abdominal aortic aneurysm. The relationship between 30-day mortality rate and 13 prespecified potential prognostic factors was investigated. The value of a published clinical prediction rule was also evaluated.

Results: The postoperative mortality rate was 5·6 per cent overall (46 deaths in 820 patients). Postoperative mortality risk was significantly associated with older age ($P = 0{\cdot}03$), higher serum creatinine level ($P = 0{\cdot}002$) and lower forced expiratory volume in 1 s (FEV_1) ($P = 0{\cdot}003$) in univariate analyses. Evidence of a relationship between age and postoperative death was weakened ($P = 0{\cdot}08$) after adjustment for creatinine level and FEV_1. The predicted postoperative mortality risk ranged from 2·7 per cent in younger patients with below average creatinine levels and above average FEV_1, to 7·8 per cent in older patients with above average creatinine levels and below average FEV_1. The published clinical prediction rule did not validate well on these data; observed risk did not correlate with predicted risk except for a small group of high-risk patients.

Conclusion: Poor preoperative lung and renal function was strongly associated with postoperative death. Age was less important once these two important prognostic factors had been taken into account. The potential for preoperative improvement in lung and renal function to reduce postoperative mortality rates should be addressed in future studies.

Paper accepted 5 December 1999

British Journal of Surgery 2000, 87, 742–749

Introduction

The postoperative mortality rate following elective surgical repair of abdominal aortic aneurysm (AAA) is considerable. National statistics indicate a 30-day postoperative mortality risk for elective surgery of over 10 per cent[1] while population-based studies from Europe and North America have observed risks of around 8 per cent[2]. Since there has been little alternative, in the long term, to surgical intervention for the treatment of AAA[3], the postoperative risks are likely to be faced by many patients sooner or later. The UK Small Aneurysm Trial[4] recently reported no difference in the all-cause mortality rate over 6 years in patients with aneurysms of diameter 4·0–5·5 cm when comparing a policy of immediate surgery with a policy of surveillance (with surgery when the aneurysm reached 5·5 cm in diameter or grew rapidly). This was due to a postoperative mortality rate of 5·8 per cent that led to a survival disadvantage soon after randomization in the early surgery group. The risk of AAA rupture in the surveillance group meanwhile was only 1·0 per cent per year.

Assessment of preoperative factors associated with postoperative risk is important for two reasons. First, it helps inform the timing of the elective repair; it is not desirable to operate when the risk of aneurysm rupture is lower than the risk of death resulting from the operation. Second, identification of preoperative risk factors may allow the prediction of postoperative risk for individual patients. This should inform decisions about the appropriateness of surgical intervention or motivate preoperative interventions designed to modify these risk factors. For example, a recent trial of preoperative optimization of oxygen delivery demonstrated that such interventions can be successful in reducing surgical mortality rate[5].

The present study used the data collected prospectively in the UK Small Aneurysm Trial[4] to investigate preoperative risk factors for postoperative death. The characteristics of patients that lead to low or high postoperative risk were identified, and the results were adjusted for the overfitting that stems from deriving and assessing a clinical prediction rule on the same data. The performance of an alternative prediction rule proposed by others on the present data was also evaluated.

Patients and methods

Of the 1090 patients in the UK Small Aneurysm Trial[4], 841 underwent aneurysm repair between September 1991 and June 1998 (when the trial closed). Eight emergency operations and 13 endovascular repairs were excluded, leaving a group of 820 patients undergoing elective open surgical repair. Patients were aged 60–80 (mean 70) years with aneurysms of diameter 4·0–7·0 (mean 4·9) cm at the time of elective repair.

Potential prognostic factors for 30-day postoperative death were investigated in patients undergoing elective aneurysm repair. A statistical analysis plan specifying a limited set of 13 prognostic variables was drawn up before inspecting the data. Variables were selected if they had previously been identified as prognostic in published studies and were deliberately limited to reduce the chance of false-positive findings. The chosen variables were: age at operation, sex, aneurysm diameter at operation (maximum anterior–posterior diameter by ultrasonography), whether the aneurysm was tender at operation, randomized group (surveillance or early surgery), forced expiratory volume in 1 s (FEV_1), serum creatinine level, evidence of myocardial ischaemia from electrocardiography (ECG) at rest, reported smoking status, hospital type (teaching or district general), graft type (straight or bifurcated as a measure of crossclamp time), surgeon volume (number of AAA operations surgeon performed during the trial) and professional rank of surgeon (consultant or specialist registrar). Measurements on all patients in the trial were taken by five trial coordinators using standard equipment to reduce measurement errors[6]. Some variables were only measured at randomization and so were not necessarily accurate at the time of aneurysm repair, particularly in the 304 patients in the surveillance group whose median delay between randomization and repair was 1·5 years. These variables were FEV_1, serum creatinine level, electrocardiographic evidence of ischaemia and smoking status. All patients were flagged at the Office of National Statistics which provided a copy of the death certificate when a patient died.

Univariate associations between 30-day mortality rate and all 13 prognostic variables were first investigated using χ^2 tests for categorical variables and t tests for continuous variables. Multiple logistic regression was then used to adjust for potential confounding effects between variables. Prognostic variables were divided into three groups: primary, biological and policy variables. Three regression models were fitted: primary variables only, primary plus biological variables and primary plus policy variables. Predicted probabilities of death were estimated after bootstrap calibration[7] of the logistic regression models. This method adjusts predictions for 'overfitting', the tendency of regression models to fit the data on which they were developed, but to be less successful on other data sets.

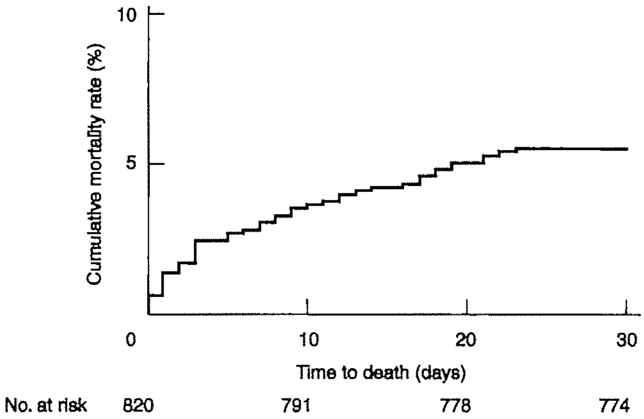


Fig. 1 Cumulative mortality rate according to time in 820 patients who underwent elective aneurysm repair

Table 1 Immediate cause of 46 postoperative deaths

Cause of death	No.	(Percentage)
Cardiac	19	(41)
Pulmonary problems*	7	(15)
Renal failure	5	(11)
Sepsis	4	(9)
Multiple organ failure	3	(6)
Pulmonary embolism	3	(6)
Haemorrhage	3	(6)
Stroke	1	(2)
Bowel infarction	1	(2)

Deaths were evaluated from death certificates. *Two chronic obstructive airway disease, five bronchopneumonia

Table 2 Relation between preoperative prognostic factors and 30-day postoperative mortality rate: univariate analyses

Variable†	Survived‡ (*n*=774)	Died‡ (*n*=46)	*P*
Primary variables			
Age at operation (years)*	69·9(4·4)	71·3(4·2)	0·03¶
Sex			0·58**
Male	647 (84)	37 (80)	
Female	127 (16)	9 (20)	
Aneurysm diameter at operation (cm)*	4·94(0·55)	5·03(0·56)	0·31¶
Tender aneurysm at operation	63 (8)	5 (11)	0·51**
Randomized group			0·36**
Surveillance	284 (37)	20 (43)	
Early surgery	490 (64)	26 (57)	
Biological variables			
FEV_1 (litres)* (18)	2·22(0·74)	1·87(0·62)	0·003¶
Creatinine (μmol/l)* (27)	107·4(30·3)	122·2(44·6)	0·002¶
Evidence of ischaemia on ECG (10)			0·48**
Possible/probable	292 (38)	20 (43)	
Unlikely	472 (62)	26 (57)	
Smoking status (2)			0·60**
Current	289 (37)	19 (41)	
Ex-smoker or never	483 (62)	27 (59)	
Policy variables			
Type of hospital			0·15**
Teaching	284 (37)	12 (26)	
District general	490 (63)	34 (74)	
Graft type (13)			0·92**
Straight	588 (77)	32 (76)	
Bifurcated	177 (23)	10 (24)	
Volume of surgery (17)*§	20·8(17)	20·0(17·1)	0·76¶
Surgeon rank (18)			0·70**
Consultant	620 (82)	37 (84)	
Registrar or specialist registrar	138 (18)	7 (16)	

*Values are mean(s.d.); †values in parentheses are number of patients for whom data are missing; ‡unless otherwise indicated values in parentheses are percentages. §Number of abdominal aortic aneurysm operations surgeon performed during the trial period. FEV_1, forced expiratory volume in 1 s; ECG, electrocardiography. ¶*t* test for continuous variables, **χ^2 test for categorical variables

Table 3 Adjusted odds ratios from multiple logistic regression for preoperative prognostic factors for death within 30 days following elective aneurysm repair

Prognostic factor	Adjusted odds ratio	*P*
Analysis 1: primary variables only (*n*=820)		
Age at operation (per decade)	2·11 (1·03–4·32)	0·04
Sex (women *versus* men)	1·19 (0·55–2·55)	0·66
Aneurysm diameter at operation (per cm)	1·27 (0·60–2·69)	0·53
Aneurysm tender at operation (yes *versus* no)	1·35 (0·46–3·97)	0·59
Randomized group (immediate surgery *versus* surveillance)	1·03 (0·42–2·52)	0·95
Analysis 2: primary variables plus biological variables (*n*=766)		
FEV_1 (per litre decrease*)	1·94 (1·18–3·22)	0·01
Creatinine (per 40 μmol/l increase*)	1·41 (1·07–1·85)	0·01
Evidence of ischaemia on ECG (probable/possible *versus* unlikely)	1·01 (0·52–1·96)	0·99
Smoking status (current *versus* ex/never)	1·02 (0·52–2·00)	0·96
Analysis 3: primary variables plus policy variables (*n*=781)		
Hospital type (district general *versus* teaching)	1·39 (0·66–2·94)	0·38
Graft type (bifurcated *versus* straight)	0·87 (0·39–1·97)	0·74
Volume of surgery (per 25 operations)*†	0·93 (0·54–1·60)	0·79
Operating surgeon's rank (consultant *versus* other)	1·46 (0·50–4·29)	0·49

Values in parentheses are 95 per cent confidence intervals. *Approximately 1·3 standard deviations of the values of the variable. †Number of operations surgeon performed during the trial. FEV_1, forced expiratory volume in 1 s; ECG, electrocardiography

To see whether the postoperative mortality risk varied between surgeons, a logistic regression model containing the primary variables and policy variables was fitted within a multilevel framework, including surgeon as a random effect[8].

A clinical prediction rule based on a patient series from the University Hospital Leiden combined with a meta-analysis of published risk factors[9] was assessed using the present data. The rule allocates scores according to the following factors: centre-specific average surgical mortality rate, age, sex, documented history of myocardial infarction (MI), congestive heart failure, electrocardiographic evidence of ischaemia, renal co-morbidity (creatinine level greater than 160 μmol/l) and pulmonary co-morbidity (chronic obstructive pulmonary disease, emphysema, dyspnoea or previous pulmonary surgery). The scores are summed for each patient and converted into a probability of postoperative death. For application to patients in the UK Small Aneurysm Trial, history of MI and pulmonary co-morbidity were taken from reported past history of disease collected from patients at initial assessment for entry into the trial. In addition, ten patients suffered an MI between entry into the trial and AAA repair. Evidence of congestive heart failure was not documented, so the patients were allocated a score of zero for this component of the prediction rule. Predicted probabilities of operative death were assessed by the *c* index[10], the chance that a patient who died after operation had a higher predicted probability of death than a patient who survived. A *c* index of 0·5 indicates random predictions.

Results

Of the 820 patients undergoing elective surgical repair for AAA, 46 (5·6 (95 per cent confidence interval 4·1–7·4) per cent) died within 30 days of surgery; most deaths occurred within 20 days (*Fig. 1*). The most common immediate cause of death was cardiac, with pulmonary problems and renal failure being the next two leading causes (*Table 1*). The in-hospital mortality rate was very similar at 5·7 per cent (47 of 820) and all in-hospital deaths occurred within 41 days of surgery. These 30-day and in-hospital mortality rates are very slightly lower than those given in the original trial[4] because emergency operations and endovascular repairs are excluded here.

Patients who died within 30 days of operation were slightly older than those who were alive at 30 days ($P = 0{\cdot}03$) (*Table 2* and *Fig. 2*) but there was no association between 30-day mortality rate and sex, size or tenderness of aneurysm, or randomized group. The adjusted analysis confirmed these findings (*Table 3*). Although a slightly higher mortality risk was observed in women and patients with larger or tender aneurysms, these effects were estimated imprecisely and were not statistically significant. The effect of aneurysm diameter on postoperative death did not vary between the randomized groups ($P = 1{\cdot}00$, test for interaction).

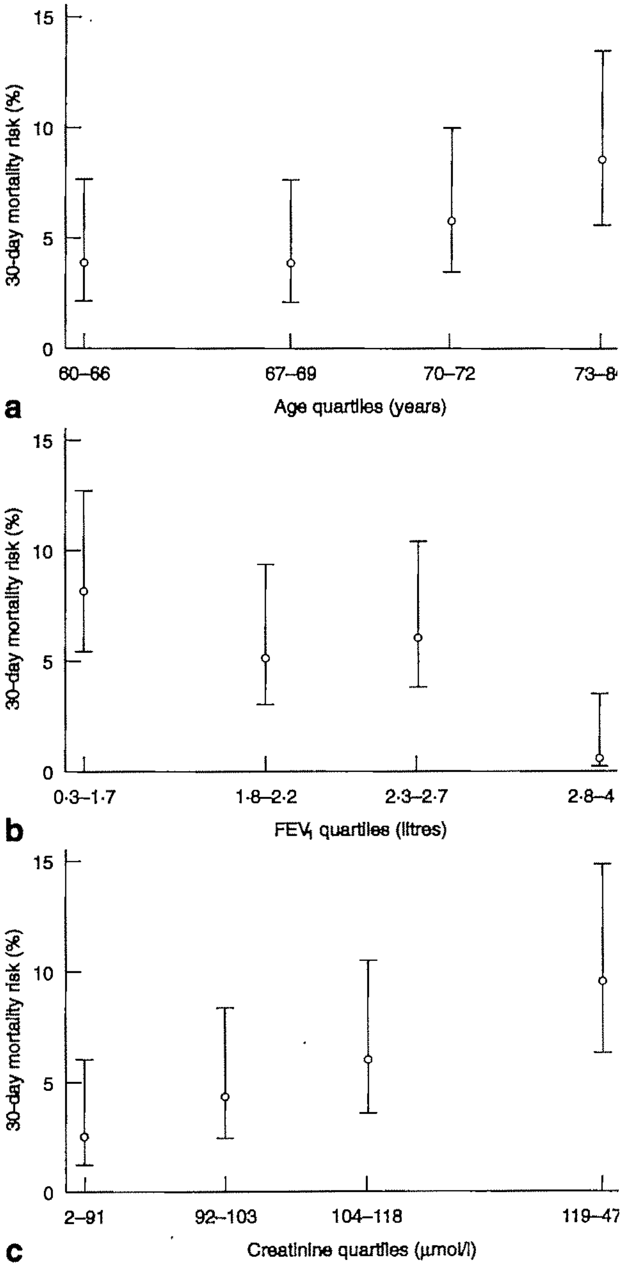


Fig. 2 Estimated 30-day postoperative mortality risk by quartiles of
a age,
b forced expiratory volume in 1 s (FEV$_1$) and
c serum creatinine level. Error bars show 95 per cent confidence intervals

Table 4 Observed and predicted risk of death within 30 days by age, forced expiratory volume in 1 s and creatinine level (below and above median)

Age (years)	FEV_1 (litres)	Creatinine (µmol/l)	Observed deaths	Observed risk (%)	Predicted risk (%)*	Predicted risk (adjusted) (%)†
60–69	2·2–4·4	2–103	1 of 116	0·9	2·2	2·7
		104–473	5 of 100	5·0	2·8	3·2
	0·3–2·1	2–103	2 of 89	2	4·1	4·1
		104–473	4 of 66	6	6·7	5·7
70–80	2·2–4·4	2–103	3 of 76	4	3·7	3·8
		104–473	10 of 112	8·9	6·0	5·2
	0·3–2·1	2–103	6 of 114	5·3	7·1	6·0
		104–473	10 of 102	9·8	10·4	7·8

Only 41 of 46 deaths are shown owing to missing values for forced expiratory volume in 1 s (FEV_1) and creatinine concentration. *From logistic regression analysis 2 (primary + biological variables); †preferred estimates, adjusted for overfitting

Lung function and renal function, as assessed by FEV_1 and serum creatinine level respectively, were significantly worse at randomization in those who subsequently died after operation ($P = 0{\cdot}003$ and $P = 0{\cdot}002$ respectively) (*Table 2*). However, electrocardiographic evidence of ischaemia and smoking status were not associated with 30-day mortality rate. The relationship between postoperative risk and both FEV_1 and creatinine level appeared to be approximately linear (*Fig. 2*). FEV_1 and creatinine level remained significantly associated with postoperative death after adjustment (both $P = 0{\cdot}01$, *Table 3*). The reduction in statistical significance was due to these variables being correlated with age (both lung function and renal function were worse in older patients). The statistical significance of the age effect was also weakened ($P = 0{\cdot}08$) after adjustment for FEV_1 and creatinine. A decrease in FEV_1 of 1 litre (about 1·3 standard deviations) approximately doubled the 30-day mortality risk whereas each increase in creatinine of 40 µmol/l (also about 1·3 standard deviations) increased the risk by approximately 40 per cent.

The percentage of patients who died within 30 days of aneurysm repair was slightly higher at district general hospitals than teaching hospitals (6·5 *versus* 4·1 per cent), but this difference was not statistically significant ($P = 0{\cdot}15$) (*Table 2*). There was no evidence of any association between postoperative survival and the other policy variables: straight or bifurcated graft, volume of surgery carried out by the operating surgeon during the trial, or surgeon rank (*Tables 2* and *3*). Additionally, in the multilevel model there was no evidence of any association between surgeon variability and postoperative risk.

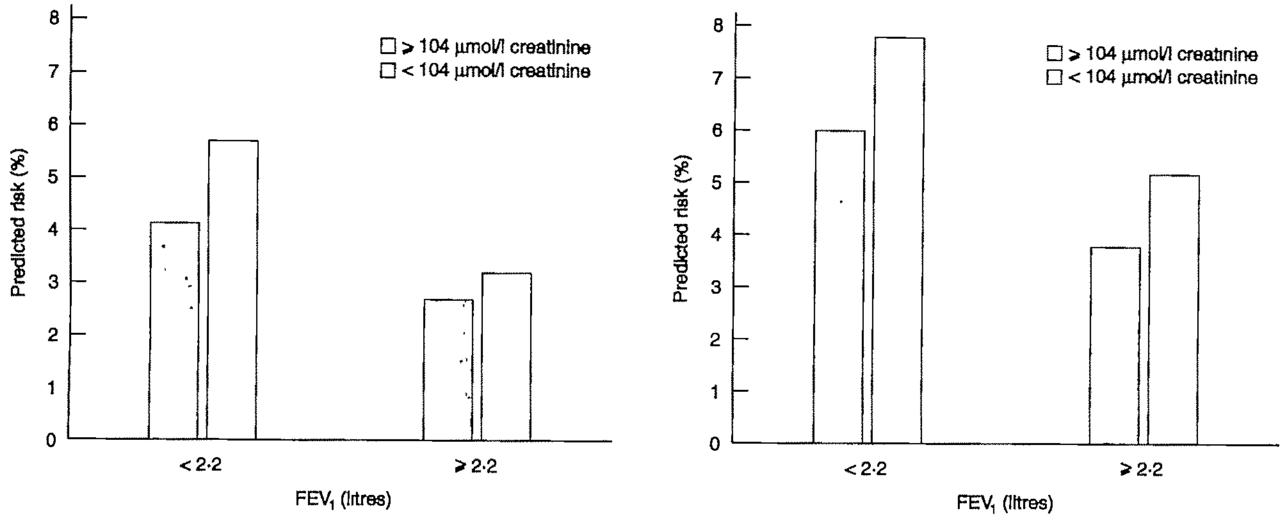
To illustrate how the three significant prognostic factors affected postoperative death, age, FEV_1 and creatinine level were dichotomized around their median values. The observed 30-day death rate varied from 0·9 per cent in younger patients with good lung and renal function to 9·8 per cent in older patients with worse lung and renal function (*Table 4*). The predicted risks from the multiple regression (analysis 2, *Table 3*) smooth out some of the random variation in the observed risks; these varied between 2·2 and 10·4 per cent (*Table 4*). The estimates of predicted risk adjusted for overfitting take into account the tendency for predictions to be less successful in new data than they appear in the current data. These varied between 2·7 and 7·8 per cent (*Table 4* and *Fig. 3*) and should be preferred for informing future patients of likely operative risk. The *c* index for predictions based on this model was 0·72, significantly different from 0·5 ($P < 0{\cdot}001$), the value that corresponds to random predictions. It decreased to 0·65 after adjustment for overfitting.

The postoperative mortality rates for groups according to the Leiden prediction rule are shown in *Table 5*. The observed 30-day mortality rate was similar in the groups at very low, low and medium risk, indicating poor discrimination of patients at lower risk. The *c* index was 0·55 and not significantly different from 0·5 ($P = 0{\cdot}13$), the value that corresponds to random predictions.

Table 5 Observed 30-day mortality rates in the UK Small Aneurysm Trial by predicted mortality risk from the Leiden prediction rule

Leiden risk group	No. of deaths
Very low (< 2)	12 of 258 (4·7)
Low (2–5)	19 of 370 (5·1)
Medium (5–10)	8 of 141 (5·7)
High (> 10)	7 of 51 (14)
Total	46 of 820 (5·6)

Values in parentheses are percentages



a Patients aged 60–69 years

b Patients aged 70–80 years

Fig. 3 Predicted 30-day mortality risk by forced expiratory volume in 1 s (FEV$_1$) and serum creatinine level (below and above median values) for patients aged
a 60–69 years and
b 70–80 years. Only 41 of 46 deaths are included because of missing values for FEV$_1$ and creatinine concentration

Discussion

The postoperative mortality risk of 5·6 per cent observed in the UK Small Aneurysm Trial was lower than that of 8 per cent reported from population-based studies, which attempt to document the outcome of elective surgery for all patients in a given catchment area. The present estimate is probably lower than the population risk owing to the upper age limit of 76 years imposed on entrants to the trial. On the other hand, the postoperative risk was higher than that in most series selectively published by individual surgeons or single surgical centres that are likely to be biased downwards[2].

There have been numerous studies reporting risk factors for postoperative death from univariate analyses but relatively few that have carried out adjusted analyses to account for correlations between risk factors[9,11,12]. The data from the UK Small Aneurysm Trial are of high quality: there are few missing values and clinical measurements were taken by five specially trained regional coordinators to reduce measurement error. The availability of serum creatinine and FEV$_1$ levels allowed these to be modelled as continuous variables, rather than defining renal insufficiency or poor lung function on the basis of a single threshold value as in most other studies[9,11,13–15].

The 30-day postoperative mortality rate did not differ between the early surgery and ultrasonographic surveillance arms of the randomized trial. The lack of evidence of an association between aneurysm size or tenderness and postoperative death lends further support to the view that surgical intervention should be delayed until the aneurysm is at least larger than 5·5 cm. Female sex could not be confirmed as a risk factor. Women are reported to be at slightly higher postoperative risk than men[9,12], but the limited sample size within the trial (and few deaths) did not afford the power to detect small effects.

The role of age in determining surgical policy is controversial[16]. Most studies, including the UK Small Aneurysm Trial, have found a univariate association between older age and higher postoperative risk. Since other risk factors for postoperative death increase with age, there was a slight weakening of the evidence for an age effect after adjusting for important prognostic variables. Other multivariable analyses have also reported an attenuated age effect[9,11,17]. Elective surgical repair should not therefore be denied to patients on grounds of age alone.

The study found that poor lung and renal function was strongly and apparently linearly related to postoperative death. Pulmonary and renal co-morbidity have been identified in other studies as important risk factors[9,11–15]. Preoperative chest physiotherapy has been shown to reduce pulmonary complications after major abdominal surgery[18] and a recent case report[19] suggested that preliminary renal stenting might reduced operative risk following AAA repair. Clinical trials with mortality endpoints are needed to evaluate preoperative interventions like these before AAA repair.

Current smoking status was not associated with postoperative outcome. Very few patients had never smoked ($n = 49$) and it appears that ex-smokers had no advantage over current smokers for surviving aneurysm repair, although the data on the length of time before surgery that patients had stopped smoking are not robust.

Cardiac co-morbidity (history of MI, congestive heart failure, electrocardiographic evidence of ischaemia) has been found to be an important risk factor in many published studies[9,11,14,15]. In the UK Small Aneurysm Trial, evaluation of fitness for surgery and cardiac function were local decisions. The only cardiac data collected were resting ECG traces and measurement of cardiothoracic ratio on chest radiograph. In this study electrocardiographic evidence of ischaemia was not a risk factor. Other parameters of cardiac function may have proved more discriminatory, but were not available. One longitudinal study[12] reported a higher operative mortality rate for patients with ischaemic heart disease before 1984 but not afterwards, and attributed this in part to 'improved management of cardiac disorders' and a major improvement in anaesthetic techniques.

There have been many attempts to provide clear clinical guidelines when considering AAA repair. The Leiden prediction rule would not have performed well on patients in the UK Small Aneurysm Trial, although it might have identified those at highest risk. Based on the findings of the UK Small Aneurysm Trial, a simpler prognostic index has been developed, based only on age, serum creatinine level and FEV_1, but this also needs to be tested prospectively.

None of the policy variables considered was found to be significant. In an audit of all operations carried out in the northern region of England[20], teaching hospitals were found to have better postoperative outcome following elective AAA repair than district general hospitals. Although a slightly higher postoperative risk was observed at district general hospitals in the present study, the difference was not statistically significant. Hospital and surgeon volumes of AAA operations have also been reported to be associated with postoperative risk[12,17], but neither surgeon volume nor rank was prognostic in this study. The willingness of centres to participate in the trial could be one explanation for the difference in findings. The increasing spread of properly trained vascular surgeons to district general hospitals implies that in many cases AAA repair does not need to be performed in a specialist centre, far from the patient's home.

Acknowledgements

The UK Small Aneurysm Trial was supported by the Medical Research Council and the British Heart Foundation with grants to the University of Edinburgh and Imperial College at Charing Cross, London. This research was supported by the BUPA Foundation with a grant to Imperial College at Hammersmith and Charing Cross Campuses, London. Details of the UK Small Aneurysm Trial participants may be found in Reference 4.

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Vascular Surgical Society

Population screening reduces mortality rate from aortic aneurysm in men

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Background: Rupture of an unsuspected abdominal aortic aneurysm is a major cause of death in men over the age of 65 years. A significant reduction in deaths is likely to result only from higher rates of detection and increased numbers of elective aneurysm repairs. Screening of men reaching the age of 65 years has been taking place in the county of Gloucestershire, UK since 1990 and the aim of this study was to investigate any change in the mortality rate from aortic aneurysm in the screened portion of the population.

Methods: Total number of deaths from all aortic aneurysm-related causes in the county's population was calculated from hospital and post-mortem records, together with computerized death certificate records, for the years 1994–1998. The overall number of aneurysm-related deaths in men aged 65–73 years, who have been progressively influenced by the screening programme, was compared with that for men of all other ages.

Results: The total number of aneurysm-related deaths in men aged 65–73 years decreased progressively year by year between 1994 and 1998; this reduction is highly statistically significant ($P < 0{\cdot}001$). No such change was observed in the unscreened part of the population.

Conclusion: Screening for asymptomatic abdominal aortic aneurysm results in a significant reduction in numbers of deaths from all aneurysm-related causes in the screened portion of the male population.

Paper accepted 16 February 2000

British Journal of Surgery 2000, **87**, 750–753

Introduction

Rupture of an abdominal aortic aneurysm (AAA) is a major cause of death in men over the age of 65 years, representing 1·4 per cent of all deaths in this age group and causing an estimated 6000 deaths annually in England and Wales[1]. Many surgical units report mortality rates for elective AAA repair of less than 5 per cent[2,3], whereas reported overall death rates from AAA rupture range from 80 to 94 per cent[4,5]. It seems unlikely that future changes in surgical or anaesthetic techniques will have a major influence on the survival of patients suffering the major physiological stress of aneurysm rupture and, in addition, many deaths continue to occur from the rupture of a previously unsuspected AAA outside hospital. The vast difference between elective surgical mortality rate and the outcome from aneurysm rupture leads to the inevitable conclusion that the overall mortality rate from this condition will be reduced only by a deliberate policy of screening for asymptomatic aneurysm, together with an increased rate of elective aneurysm repair.

Screening for asymptomatic AAA is currently regarded by many UK health authorities as an intervention of unproven value. It remains a major challenge in modern vascular surgery to prove its efficacy in order to encourage the funding of further screening programmes. One randomized trial in the UK has already suggested a survival advantage in men offered screening for asymptomatic aneurysm. In 1995, Scott *et al.*[6] published data from the Chichester area which showed a small but significant reduction in both the incidence of aneurysm rupture and overall aneurysm-related deaths in a group of 3205 men offered aneurysm screening, compared with a control group without screening. More recently, results from the aneurysm screening programme in Huntingdon, UK showed a reduction of about one half in the risk of aneurysm rupture in screened patients, although no calculation was made of the overall effect on community mortality rate in this study[7]. A much larger multicentre randomized trial of aneurysm screening has now started in the south and east of England but results are not expected until at least the year 2001. Screening of 65-year-old men for the presence of asymptomatic AAA has been taking place in Gloucestershire since 1990. The aim of the present study was to assess the influence of this programme on overall community mortality rate from all aneurysm-related causes in men offered screening.

Patients and methods

Full details of the design of the Gloucestershire Aneurysm Screening Programme have been published previously[8,9] and a total of 96 of the county's 97 general practices has been involved since its introduction. Screening involves abdominal ultrasound examination of men reaching the age of 65 years, carried out by a mobile team who visit each of the participating general practices annually. Men registered with each participating practice are invited to attend for screening on the basis of their year of birth; in 1990, men born in 1925 were invited and each birth year from 1925 to 1933 has been targeted in sequence from 1990 to 1998. Men aged over 65 years when the programme started in 1990 have not been involved in the programme.

This method of selection has resulted in a gradually increasing cohort of screened men within the county's total population of approximately 520 000. In 1990, only men born in 1925 were offered screening. By the end of 1998, this original group of 65 year olds had reached the age of 73 years, and all men in the county aged between 65 and 73 years had been offered an ultrasound scan.

Total community death related to AAA was measured by including deaths from ruptured AAA occurring outside hospital, deaths where the diagnosis of a ruptured AAA was made during a hospital admission and deaths following elective AAA repair. These data were obtained by a review of all hospital admission records for the county's two main district general hospitals, post-mortem records from the two hospitals, operating theatre and intensive care unit records, and the Vascular Unit database. Details of all death certificates for Gloucestershire residents from 1994 onwards were available from a computer database; this source provided a final verification of the authors' data, as well as identifying a number of deaths from ruptured AAA certified by the general practitioners without hospital admission or post-mortem examination. Care was taken to include only deaths related to atherosclerotic AAA and to exclude those attributed to aortic dissection or to rupture of a thoracic aortic aneurysm.

Results

Table 1 summarizes the work of the screening programme in its first 9 years. Of note is the high attendance rate (84 per cent), possibly attributable to the fact that screening is based in the general practitioner's surgery. Approximately one half of the 446 aneurysms of 4·0 cm or greater that were discovered were present at the initial screening examination. The remainder grew to this size, during annual follow-up of aortas of between 2·6 and 3·9 cm in diameter.

Fig. 1 shows that the total number of aneurysm operations on men increased only slightly between 1991 and 1998. More importantly, the proportion of annual operations carried out electively, particularly on screen-detected aneurysms, has grown since screening started. At the end of 1998, 184 aneurysms detected in the screening programme had undergone elective repair, 179 routinely and five urgently because of the development of symptoms of pain or tenderness. Median diameter of the 179 aneurysms undergoing planned repair was 5·5 (range 3·9–13·4) cm. Only 15 aneurysms were smaller than 5·0 cm in diameter at the time of surgery and only two were smaller than 4·5 cm in diameter. One of these small aneurysms was operated on because of an associated 6·0-cm iliac aneurysm and the

Table 1 Summary of workload for the Gloucestershire Aneurysm Screening Programme, 1990–1998

County population	520 000
Birth years targeted	1925–1933
Invitations	24 479
Scans	20 633 (84% attendance)
Aortas > 4·0 cm discovered	446
Elective aneurysm operations	184

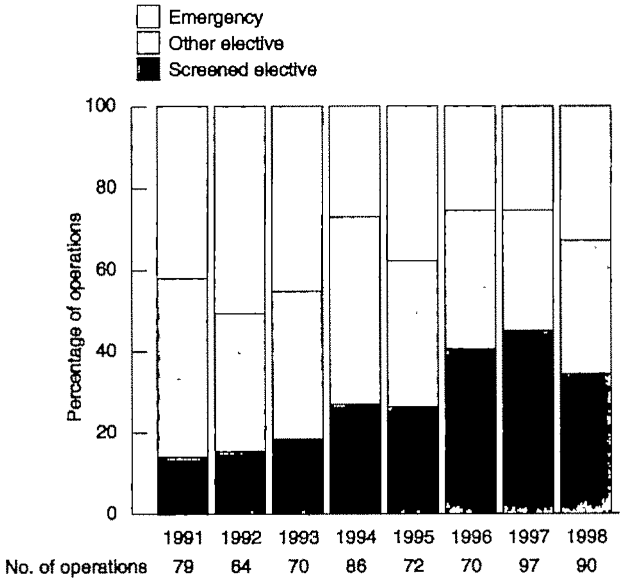

Fig. 1 Total number of abdominal aortic aneurysm operations on men in Gloucestershire, 1991–1998

indication for surgery in the other was distal embolization. Seven operations were performed in hospitals outside Gloucestershire, with a single postoperative death. The 177 operations within the county resulted in seven postoperative deaths (mortality rate 4 per cent).

Fig. 2 illustrates the total number of deaths in men from all aneurysm-related causes from 1994 to 1998, the period for which full death certificate information was available. Deaths occurring each year in men aged between 65 and 73 years, the age range progressively influenced by screening, are shown separately from those occurring at all other ages. Total aneurysm-related deaths in the community in men aged between 65 and 73 years decreased significantly year on year ($P < 0.001$, χ^2 test for trend). While aneurysm-related deaths in the targeted 65–73-year-old population showed a 66 per cent reduction between 1994 and 1998, total aneurysm-related deaths in men outside this age group ranged between 32 and 48 per year in an apparently random fashion.

A total of 83 aneurysm-related deaths was recorded between 1994 and 1998 in men aged between 65 and 73 years. Ten of these followed elective aneurysm repair, eight in screened patients and two in patients whose aneurysm had been detected incidentally (*Fig. 2*). Overall, 33 of these 83 deaths occurred in men who, according to their date of birth, should have been offered an appointment for aneurysm screening. All but three had been invited to a screening session and 20 had attended (*Table 2*). *Table 2* highlights, in particular, the problem of screen-detected aneurysms in patients considered unfit for elective repair (nine deaths from subsequent aneurysm rupture) and the higher risk of death from aneurysm rupture in patients who did not accept their invitation for screening. Of the 33 aneurysm-related deaths in men eligible by age for screening, 13 occurred in the 16 per cent of the population who, for one reason or another, did not attend a screening session.

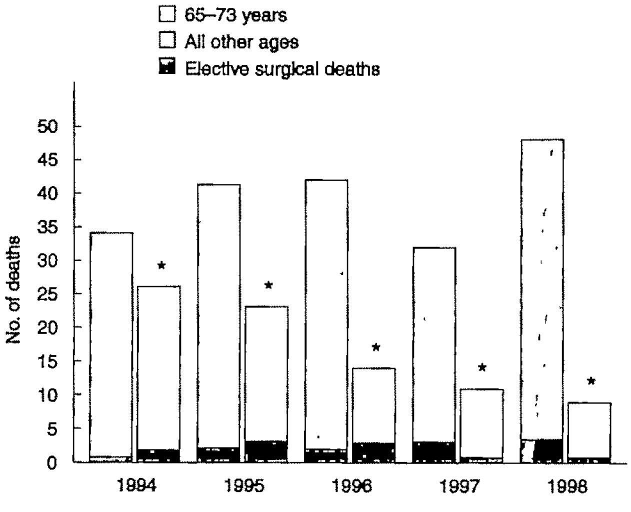

Fig. 2 Total number of aneurysm-related deaths in men in Gloucestershire, 1994–1998. $^*P < 0.001$ (χ^2 test for trend)

Table 2 Analysis of 33 aneurysm-related deaths in men eligible for screening

	No. of deaths
Screened men	20
Following elective aneurysm surgery	8
AAA rupture in patients deemed unfit for elective repair	9
AAA rupture; defaulted from follow-up after initial detection	1
AAA rupture 2 weeks after detection while awaiting admission	1
AAA rupture between scans* at diameter of 4·8 cm	1
Non-screened men within the age range for screening	13
Failed to attend after invitation for screening	10
Patient from county's non-participating general practice	1
Moved to Gloucestershire after the age of 65 years	1
Not recorded on the general practice age/sex register	1

*Scans at intervals of 6 months. AAA, abdominal aortic aneurysm

Discussion

This is an observational study rather than a randomized trial. However, there is no reason to suspect any influence other than aneurysm screening on the total number of deaths from aortic aneurysm during the period of the study. The relevant population is defined by those patients registered to general practices within the county of Gloucestershire and there is no evidence of any major demographic changes in the county between 1994 and 1998. It appears, therefore, that these results are the first clear demonstration of a beneficial effect of aneurysm screening in a large, geographically defined population. The male population offered screening had a significant, progressive reduction in all deaths related to aortic aneurysm which was not observed in the remainder of the population. This trend should continue as the size of the screened male cohort expands year by year to encompass the age range at which the incidence of aneurysm rupture is at a peak, i.e. 70–80 years of age.

The worth of a screening programme for AAA can best be measured in terms of total number of deaths in the community, including both deaths occurring outside hospital and those resulting from increased elective surgical activity. In this way any bias in selecting patients for elective aneurysm repair is removed and the practical difficulties inherent in the accurate detection and follow-up of large numbers of patients are incorporated. The accuracy of any calculation of death from AAA rupture outside a hospital setting is limited by the accuracy with which such deaths are recorded on death certificates. Gloucestershire has an overall post-mortem rate of approximately 18 per cent, similar to that of many other areas in the UK. It is highly likely that a number of deaths from AAA rupture goes unrecognized and unrecorded each year. However, there is no reason to suspect that the number of such missed diagnoses has changed during the study sufficiently to alter the validity of the findings. In fact, it might be expected that increased public and professional awareness of the condition, because of the screening programme, would increase the likelihood of ruptured aneurysm being considered the cause of sudden death, thereby making it more difficult to demonstrate a reduction in the total number of deaths.

It is clear, from this and other similar studies, that screening of the population for asymptomatic AAA can reduce both the risk of rupture and the overall risk of death from this condition. Three other important messages are also clear. First, elective operative death becomes a significant factor in the outcome of screened patients and must be kept to a minimum if the benefits of a screening programme are to be realized; Scott *et al.*[10] have investigated the relationship between an individual unit's mortality rate for elective aneurysm repair and the size of aneurysm for which elective repair is justified. Second, the detection of an asymptomatic aneurysm in a patient with other significant medical problems presents a major dilemma since aneurysm rupture remains a likely cause of death despite coexisting medical conditions. Difficult decisions are needed about the level of elective surgical risk that is acceptable in such patients. In the future, endovascular techniques may offer lower-risk operations for patients with significant cardiac or respiratory disease but at present this is unproven. Third, the data in *Table 2* suggest that the risk of death from aneurysm rupture is at least twice as high in non-attenders than in screened patients. As in many health screening programmes, non-attenders may be at a higher than average risk of both exhibiting and dying from the targeted condition (the 'healthy volunteer' effect). For maximum community benefit, attendance rates at screening sessions must be high and specific targeting of at-risk groups may be justified.

The effectiveness of population screening for AAA in terms of reducing deaths from aneurysm rupture is confirmed. No attempt has been made in this study to calculate the cost of the programme. Sufficient data now exist for such calculations to be made in a realistic manner rather than relying on unsatisfactory mathematical models, and should enable aneurysm screening to be given appropriate funding priority.

Acknowledgements

The authors thank Mrs Sue Jones, Gloucestershire Health Authority, for help with the collection of death certificate data, Mr Chris Foy for help with statistical analysis, all Gloucestershire general practitioners for their cooperation in the programme and the radiographers who performed the ultrasound scans.

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Vascular Surgical Society

Randomized, multicentre, double-blind, placebo-controlled trial of the use of aprotinin in the repair of ruptured abdominal aortic aneurysm

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Background: The use of aprotinin in cardiac surgery reduces blood transfusion requirements. The aim of this trial was to see whether the same benefit applies in the repair of ruptured abdominal aortic aneurysm (AAA).

Methods: In this prospective, randomized trial, nine centres with local ethics committee approval recruited 77 patients with a ruptured AAA. A bolus of aprotinin 2×10^6 units, followed by an infusion of $0{\cdot}5 \times 10^6$ units every 30 min, was administered to 38 patients, and 39 received a placebo infusion. The quantity of blood products transfused during surgery and in the first 12 h after operation was noted, along with the incidence of complications, mortality rates and length of hospital stay.

Results: Seventeen of the 38 patients who received aprotinin and 17 of the 39 given placebo died within 30 days (overall mortality rate 44 per cent). The median amount of blood given to the aprotinin group after operation was 1 (range 0–14) unit, while for the placebo group it was 3 (range 0–13) units ($P = 0{\cdot}02$). However, the difference in the total number of units of blood transfused did not reach significance (10 (range 2–29) *versus* 14 (range 4–38) units respectively).

Conclusion: The use of high-dose aprotinin during the repair of a ruptured AAA reduced blood transfusion requirements in the first 12 h after operation, but had no significant effect on the overall blood transfusion requirement.

Paper accepted 12 February 2000

British Journal of Surgery 2000, 87, 754–757

Introduction

Typical operative mortality rates associated with the repair of a ruptured abdominal aortic aneurysm (AAA) range between 41 and 57 per cent[1–4]. This mortality rate has remained high despite a higher proportion of operations being performed by vascular surgeons and improvements in intensive care facilities. The co-morbidity of the individual, postoperative complications, excessive blood loss and the requirement for multiple blood products affect survival[1,4]. Most patients who die in intensive care do so after a prolonged downward spiral of multiple organ failure, often precipitated by a coagulopathy and initiation of the systemic inflammatory response.

Aprotinin, a low molecular weight, broad-spectrum protease inhibitor, has many modes of action. It appears to preserve platelet function[5], to inhibit plasmin and kallikrein, and to reduce the activation of neutrophils and complement, inhibiting fibrinolysis. Aprotinin has been used to reduce perioperative bleeding; its use is associated with a significant decrease in blood transfusion requirements during reoperative cardiac surgery[6]. The use of aprotinin in the elective repair of AAA reduces the blood loss in suction drains, but not the total blood loss or transfusion requirement[7]. Administration of aprotinin during the repair of a ruptured AAA may inhibit fibrinolytic activation, thereby reducing the incidence of coagulopathy and ensuing multiple organ failure. This prospective trial was established to measure the effect of aprotinin on morbidity and mortality rates, and blood product requirements in patients undergoing emergency repair of a ruptured AAA.

Patients and methods

All members of the Joint Vascular Research Group, a collaborative group of British and Irish consultant vascular surgeons who organize multicentre trials within vascular surgery, were invited to submit patients to the study. Each participating centre obtained local ethics committee approval. The committees acknowledged that obtaining written informed consent in an emergency situation could be difficult and recommended that it should be sought from either the patient or family when possible. Written consent was obtained from only a small proportion of patients. Because of the difficulty in obtaining informed consent, several local ethics committees refused to sanction the trial, which was begun before the introduction of the Multicentre Regional Ethics Committee (MREC) system.

Bayer PLC (Newbury, UK) supplied the aprotinin and a single pharmacist undertook the preparation of all samples in the sterile production facility at the Royal Hallamshire Hospital (Sheffield, UK). Bottles were prepared containing either 2×10^6 units of aprotinin in 200 ml saline or $0{\cdot}5 \times 10^6$ units of aprotinin in 50 ml saline. Identical bottles of sterile 0·9 per cent saline were also prepared. Bottles were numbered and sent to the participating centres, where they were kept in the theatre fridge. The randomization was in permuted blocks of ten, ensuring approximately equal numbers of each treatment within individual centres. Aprotinin or placebo was administered according to the randomization list drawn up by the pharmacist; the code for determining the contents of each bottle remained with the pharmacist until the end of the trial.

The inclusion criteria for the trial were the clinical diagnosis of a ruptured AAA, i.e. hypotensive collapse associated with a pulsatile abdominal mass, and the acquisition of written, informed consent when possible. Patients were excluded from the study if they had any previous exposure to aprotinin, known renal failure with a serum creatinine level greater than 150 μmol/l, or known respiratory or cardiac failure requiring hospital admission within the previous year. Patients were to be withdrawn from the study if the AAA was not ruptured at laparotomy or if any significant pre-existing renal, cardiac or respiratory failure was subsequently discovered.

An intravenous bolus of aprotinin 2×10^6 units (or similar volume of placebo) was administered as soon as possible after the patient reached theatre and a further dose of $0{\cdot}5 \times 10^6$ units (or placebo) was given every 30 min during the operation, to a maximum total dose of 4×10^6 units.

Along with demographic details and co-morbid features, preoperative blood results were recorded, as well as the operative findings and the type of repair undertaken. The number of units of blood, fresh frozen plasma (FFP) and platelets administered during the operation (encompassing time of admission to completion of surgery) and in the first 12 h following operation were recorded. The incidence of postoperative complications, including respiratory failure defined as requiring ventilation beyond 48 h or reintubation, renal failure defined as requiring haemofiltration or haemodialysis, or death within 30 days was noted, as were the length of intensive care unit and hospital stay. Statistical analysis utilized the SPSS package (SPSS, Chicago, Illinois, USA) and the Kruskal–Wallis test to examine the differences between the number of blood products transfused.

A power calculation based on the benefits in cardiac surgery was performed before the commencement of the trial. In cardiac reoperative surgery using aprotinin there was an eightfold reduction in blood transfusion requirements. Such a dramatic effect seemed unlikely in patients with an AAA, when a survey conducted before the trial showed mean blood transfusion requirements of 6·9 litres during the repair of a ruptured AAA. Assuming a 50 per cent reduction in blood loss, to demonstrate a significance level of 5 per cent with a power of 90 per cent, 50 patients were required in each group.

Results

Nine centres recruited 79 patients over a 42-month period (December 1994 to June 1998). Two were withdrawn at laparotomy because the AAA was found not to have ruptured. No patient was withdrawn from the trial after surgery on the basis of any pre-existing cardiac, renal or respiratory disease. The age range was 52–88 (median 73) years and 66 patients were men. Aprotinin was administered to 38 patients and placebo to 39. The incidence of risk factors in the two groups was similar (*Table 1*). Thirty-four patients (44 per cent) died within 30 days, 17 of those receiving aprotinin and 17 in the placebo group. The causes of death and the incidence of other complications are listed in *Table 2*. Specifically, the incidence of thromboembolic complications was not higher in the aprotinin group.

Table 1 Incidence of preoperative risk factors in patients undergoing repair of a ruptured abdominal aortic aneurysm

	Aprotinin ($n=38$)	Placebo ($n=39$)
Median (range) age (years)	74 (56–88)	73 (52–86)
Sex ratio (M : F)	30 : 8	36 : 3
Hypertension	19	15
Ischaemic heart disease	12	11
Cardiac arrhythmia	4	2
Stroke/TIA	2	5
Claudication	4	2
Previous arterial surgery	1	1
COAD	4	8
Smoker	14	17

TIA, transient ischaemic attack; COAD, chronic obstructive airways disease

Table 2 Causes of death within 30 days of surgery for ruptured abdominal aortic aneurysm and incidence of other complications

	Aprotinin	Placebo
Cause of death		
Operation abandoned (bleeding)	5	1
Coagulopathy	0	3
Multiple organ failure	4	6
Colonic ischaemia	0	1
Acute renal failure	2	0
Adult respiratory distress syndrome	4	1
Myocardial infarction	1	2
Stroke	0	3
Diverticular disease	1	0
Complications		
Acute ischaemia requiring embolectomy	11	9
Compartment syndrome	1	0
Paralytic ileus	3	1
Laparotomy (for adhesions)	0	1
Angina	0	1
Cardiac arrhythmia	1	1
Congestive cardiac failure	1	1
Wound infection	1	0
Rash	1	0
Clot retention	1	0

Table 3 Blood products transfused during and after surgery for ruptured abdominal aortic aneurysm

	Aprotinin	Placebo	*P*
Perioperative transfusion (units)			
Blood	7 (0–20)	10 (2–32)	n.s.
FFP	2 (0–40)	4 (0–12)	n.s.
Platelets	0 (0–12)	0 (0–10)	n.s.
Postoperative transfusion (units)			
Blood	1 (0–14)	3 (0–13)	0·02
FFP	2 (0–22)	0 (0–10)	n.s.
Platelets	0 (0–24)	0 (0–12)	n.s.
Total transfusion (units)			
Blood	10 (2–29)	14 (4–38)	0·053
FFP	4 (0–69)	4 (0–19)	n.s.
Platelets	0 (0–36)	6 (0–18)	n.s.

Values are median (range). FFP, fresh frozen plasma; n.s., not significant
Statistical test used: Kruskal-Wallis

Significantly less blood was given to the aprotinin group in the 12 h following surgery: a median of 1 (range 0–14) *versus* 3 (range 0–13) units ($P = 0·02$) (*Table 3*). However, the difference in the total number of units of blood given to each patient just failed to reach statistical significance: 10 (range 2–29) units in the aprotinin group compared with 14 (range 4–38) units for placebo ($P = 0·053$). There was no difference between the two groups in the number of units of platelets or FFP given.

Table 4 Recorded incidence of proven coagulopathy at the time of admission for ruptured abdominal aortic aneurysm and quantity of blood transfused

	Blood transfused (units)		
	During surgery	After surgery	Total
Aprotinin ($n = 25$)			
Deranged clotting	9 (5–18)	1 (0–14)	12 (5–29)
Normal clotting	6 (0–20)	1 (0–8)	2 (2–28)
Placebo ($n = 25$)			
Deranged clotting	10 (3–25)	2 (0–13)	14 (4–27)
Normal clotting	9 (2–32)	4 (0–8)	12 (5–38)

Values are median (range)

The presence of significant coagulopathy on admission was recorded in only 50 (65 per cent) of the 77 patients before surgery, and the postoperative results were described in only 38 (76 per cent) of these 50 (49 per cent of all patients). The distribution of the number of units of blood given in these two groups is shown in *Table 4*.

The median length of stay in the intensive care unit was 3 days for patients given aprotinin and 3·5 days for those given placebo; the corresponding length of hospital stay was 12 and 15 days (*P* not significant).

Discussion

The overall mortality rate of 44 per cent compares favourably with previous reports about ruptured AAA, and probably reflects the fact that all surgery was undertaken in vascular units.

One criticism of this study is the length of time it took for nine centres to recruit 77 patients. There were frequent delays in recruitment when the shelf-life of the prepared aprotinin expired. Time was lost as more batches were prepared and distributed; this happened on three occasions during the trial. These difficulties led to fewer patients being recruited than originally intended. As recruitment was difficult to re-initiate each time a new batch of aprotinin was prepared and distributed, it was decided to end the trial after the last of the prepared bottles in the third batch had been administered. Since the original power calculation suggested that 100 patients needed to be included, the insufficient recruitment raises the possibility of a type II statistical error.

Some local ethics committees would not give approval to the trial because of the problems in obtaining informed consent from a collapsed patient. Specific guidance regarding informed consent in this circumstance was sought from the Department of Health, but the circulation of a response that supported the trial failed to influence the decisions of most local ethics committees. Without clear guidelines, which now fall under the jurisdiction of the MREC, it will not be possible to undertake future multicentre trials in collapsed patients.

A distinction was made between perioperative and postoperative blood transfusion, as the cause of blood loss in these two intervals is often quite different. Most blood loss during surgery is related to obtaining control of the aorta and the subsequent anastomoses, while transfusion given after the patient reaches the intensive care unit is largely governed by physiological parameters and blood results. These are judged by individual anaesthetists and surgeons, and could not be prescribed within a trial protocol. However, it was felt that transfusion within the immediate postoperative period was likely to represent the need to correct any coagulopathy, and it was of value to measure specifically since this was potentially the time when any benefit from aprotinin might be demonstrated.

Five patients in the aprotinin group died during surgery, either because of difficulties in gaining control of the aorta or anastomotic problems. These patients received between 5 and 18 units of blood. While they clearly did not receive any blood after operation, removing this small group of patients from the analysis made no difference to the statistical significance.

It had been anticipated that patients with a proven coagulopathy before the repair of a ruptured AAA might have more benefit from aprotinin. Small numbers of patients in each subgroup meant that it was impossible to make any statistically meaningful conclusions, although the results suggested that less blood was required if aprotinin was given to patients with a proven coagulopathy.

Identification of any technique to reduce blood loss may have a significant effect on the mortality rate associated with ruptured AAA, and it is disappointing that aprotinin did not have the same effect in aortic as in cardiac surgery. The benefit in cardiac patients has been attributed to an effect on the membrane oxygenator, which can lead to fibrinolysis. It was thought that a similar effect might occur in ruptured AAAs as the blood crosses the graft. A recent study measuring levels of tissue plasminogen activator, plasminogen activator inhibitor and prothrombin fragment showed no difference between patients undergoing surgical repair of ruptured or non-ruptured AAA, concluding that rupture was associated with inhibition of systemic fibrinolysis[8]. This may, in part, explain the failure to demonstrate any benefit of aprotinin for ruptured AAA.

While the results of the present study suggested a reduction in postoperative transfusion requirements in patients with a ruptured AAA given aprotinin, this difference was minimal and may have been compromised by a type II statistical error. No significant difference was demonstrated in the overall blood transfusion requirements. In the absence of any positive effect on morbidity or mortality rates, routine use of aprotinin during the repair of a ruptured AAA cannot be recommended.

Acknowledgements

The authors submit this work on behalf of all the contributing vascular surgeons: Mr J. J. Earnshaw, Gloucestershire Royal Hospital; Mr S. Parvin, Royal Bournemouth Hospital; Professor M. Horrocks, Royal United Hospitals, Bath; Mr R. Naylor, Leicester Royal Infirmary; Mr D. Ratliff, Northampton Hospital; Mr R. N. Baird, Bristol Royal Infirmary; Professor C. V. Ruckley and Mr A. McL. Jenkins, Edinburgh Royal Infirmary; Professor A. Mansfield, St Mary's Hospital, London; and Professor R. Wood, Mr P. Chan, Mr R. Lonsdale and Mr J. Michaels, Sheffield Vascular Institute. The authors are also grateful to Mr Roger Brookes, Production Pharmacist at the Royal Hallamshire Hospital, Sheffield for preparing and distributing the samples, and to Bayer PLC for supplying the aprotinin.

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Two-year results of a randomized controlled trial of rifampicin-bonded extra-anatomic Dacron grafts

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Paper accepted 20 February 2000

Introduction

Infection complicates a significant number of prosthetic arterial reconstructions, resulting in major morbidity and mortality. The present study was a multicentre randomized controlled trial of rifampicin-bonded, gelatin-coated Dacron grafts for extra-anatomic bypass. The methods and early results have been reported previously[1]. This paper describes results after 2 years' follow-up.

Patients and methods

Patients were randomized to either a rifampicin-bonded graft or no-antibiotic graft. Gelatin-coated Dacron grafts (8–10 mm) were employed in both groups (Gelsoft or Gelseal; Sulzer Vascutek, UK). Bonded grafts were soaked in rifampicin solution 1 mg/ml for 15 min before insertion. All other measures were controlled within each centre, including three-dose perioperative antibiotic prophylaxis.

The main endpoint of the trial was a serious wound infection (Szilagyi grade III) involving dehiscence of the wound with involvement of the graft or fabric graft infection.

Results

Some 123 patients received rifampicin-bonded grafts and there were 134 controls. There were 178 men and 79 women, of median age 69 (range 43–92) years. Follow-up to 2 years or death was available for 223 of 257 patients. Sixty-five patients have died, four as a consequence of graft infection and the remainder from unrelated causes. The mortality rate was 8.9 per cent after 1 month, 15.6 per cent after 6 months, 21.7 per cent after 1 year and 30.7 per cent after 2 years.

By 2 years ten patients had a serious wound or graft infection (six bonded, four unbonded) resulting in an overall infection rate of 4·5 per cent. The graft fabric was infected in eight of the ten patients and all involved groin wounds. Nine infections occurred within 6 months of operation and were the result of continued sepsis in a wound that never healed after initial surgery. Only a single late infection (12 months after operation) has been recorded so far.

Bacteriological analysis was available in eight of ten infections, with positive isolates in five patients. All but a single infection with methicillin-resistant *Staphylococcus aureus* (MRSA) were sensitive to rifampicin.

In the previous analysis, preoperative risk factors such as gangrene, diabetes and steroid use were significantly associated with minor wound complications[1]. In this report six of the ten patients with a major wound or graft infection were in the group with one or more preoperative risk factors for infection, compared with four in the group with no risk factors.

Major wound and graft infection affected three (2·0 per cent) of 148 femorofemoral crossover grafts, five (6 per cent) of 81 axillobifemoral grafts and two of 28 cross iliofemoral grafts. There were no significant advantages shown for rifampicin bonding in any of these groups.

Discussion

Despite studies on almost 3000 patients, there remains no scientific evidence that rifampicin bonding reduces the incidence of vascular graft infection. An Italian study of 600 patients with aortofemoral grafts reported 2-year results: there were five infections in patients with bonded grafts (1·7 per cent) compared with seven (2·3 per cent) with unbonded grafts[2]. A large European study examined 2400 patients having aortofemoral or femorofemoral bypass and found that rifampicin bonding did significantly reduce the incidence of minor and intermediate wound infections from 4·4 to 2·9 per cent[3], similar to early results from the present trial[1]. No late results have been reported. The findings of these trials and the present investigation may be the result of an inadequate antibiotic delivery system (wrong drug or dose of drug) or the wrong concept, i.e. the cause of graft infection is more complicated than originally thought. All three published randomized trials used rifampicin in a concentration of 1 mg/ml based on previous research. New experimental evidence suggests that a higher concentration of 10–60 mg/ml may be more effective[4]. Rifampicin is active against many of the pathogens causing vascular graft infection, although there are reservations about its efficacy against MRSA.

The role of antibiotic bonding remains uncertain. *In situ* replacement with a bonded graft has become standard treatment for selected patients with graft infection and Strachan[5] has suggested that prophylactic use in 'high-risk' patients is justified. Results from the present study fail to support this contention. Although preoperative risk factors could be used to predict early postoperative wound problems[1], they did not predict graft infection.

The causes of graft infection are perhaps too complex for a single, simple solution. Other antibiotic/antiseptic-bonded grafts are being introduced and these should be tested in clinical trials. Meanwhile surgeons cannot rely on antibiotic bonding to prevent vascular graft infection.

Acknowledgements

The authors thank the surgeons and their teams from the Joint Vascular Research Group who contributed patients to this study (for a full list see *Br J Surg* 1998; **85**: 1378–81). The authors and the Joint Vascular Research Group thank Sulzer Vascutek Ltd for generous financial support.

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Apolipoprotein E genotype is associated with differential expansion rates of small abdominal aortic aneurysms

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Background: The common polymorphism of the apolipoprotein E (APOE) gene is associated with differential risk of atherosclerosis; the gene could be a candidate gene in abdominal aortic aneurysms (AAA).
Methods: APOE genotypes were determined in 57 men aged 65–73 years with a small AAA (30–50 mm). The patients were included in a population ultrasonographic screening programme and were followed with at least two examinations during an interval of 2–4·5 years. The AAA expansion rates in patients with four different APOE genotypes were studied, with adjustment for initial AAA size and smoking.
Results: APOE genotype was a significant determinant of AAA expansion rate ($P = 0{\cdot}001$). The adjusted mean (95 per cent confidence interval) rate was 2·1 (1·7–2·6) mm/year in 31 men with genotype E3E3, 1·3 (0·7–1·9) mm/year in 17 men with E3E4, 3·1 (2·0–4·1) mm/year in six men with E2E3 and 4·2 (2·7–5·6) mm/year in three men with E2E4. The mean expansion rate was 2·2 (1·5–2·8) mm/year in non-smokers and 3·0 (2·5–3·6) mm/year in smokers ($P = 0{\cdot}014$).
Conclusion: APOE genotype seems to influence AAA expansion rate, but the effects of the individual genotypes, in particular E3E3 and E3E4, are contradictory when compared with the effects of the genotypes on risk of atherosclerosis.

Paper accepted 16 February 2000

British Journal of Surgery 2000, 87, 760–765

Introduction

Apolipoprotein E (APOE) is a glycoprotein of 299 amino acids and a constituent of all human lipoproteins except low density lipoproteins (LDLs). It plays a key role in triglyceride and cholesterol metabolism by mediating the removal by the liver of remnants of triglyceride-rich lipoproteins via the heparan sulphate proteoglycan–LDL receptor-related protein and LDL receptor pathways, and by modulating hepatic very low density lipoprotein production and lipolysis of triglyceride-rich lipoproteins mediated by lipoprotein lipase in peripheral tissues[1–3]. APOE can also redistribute lipids within tissue among the various cells, and serves as the principal lipid transport vehicle in cerebrospinal fluid. Furthermore, the protein has emerged as an important molecule in biological processes not related to lipid transport functions, including basic neurobiological processes, immunoregulation[2,4] and possibly bone metabolism[5].

The APOE gene is on chromosome 19q13.2 and three codominant alleles, APOE*2, APOE*3 and APOE*4, are common in most populations[6–8]. The structures of the three encoded protein isoforms vary in subtle, but important, ways[2,9]. There are differences between APOE genotypes in plasma lipid and apolipoprotein levels within the normal ranges. Thus, compared with individuals with the most common genotype, E3E3, carriers of the APOE*2 allele tend to have lower plasma levels of cholesterol and apolipoprotein B (APOB), and higher levels of APOE and triglycerides. In contrast, carriers of APOE*4 tend to have higher cholesterol, APOB and triglyceride levels, but lower APOE[6,7,10,11].

In accordance with the effects of APOE*2 and APOE*4 on plasma lipoprotein levels, autopsy studies of younger people indicate that APOE*2 carriers tend to have fewer atherosclerotic lesions (fatty streaks, plaques and complicated lesions) in the aorta and the coronary arteries than E3E3 genotypes, whereas APOE*4 carriers tend to have more lesions[12–14]. APOE*4 carriers also tend to develop more severe coronary artery disease, as determined by angiography, than individuals without APOE*4, and to have a higher risk of clinical coronary heart disease[15–17]. In some cases, however, APOE*2 is strongly associated with atherosclerosis, since homozygotes may develop type III hyperlipidaemia. This lipid disorder also develops in carriers of various rare APOE alleles and in individuals with APOE deficiency[18]. The latter condition can be reproduced in APOE knockout mice, which has turned out to be a valuable animal model for studying the role of APOE in atherosclerosis and in other diseases[2,18,19].

The tendency of abdominal aortic aneurysms (AAAs) to cluster in families suggests that there may be a genetic component in the aetiology of the disease[20–24]. This putative genetic component may relate to atherosclerosis and the genetic polymorphism of APOE. Therefore, the APOE genotypes were determined in 57 men with a small AAA, who had been followed with annual ultrasonographic examination over 2–4·5 years. The aim was to investigate if aneurysm expansion rates differed between APOE genotypes.

Patients and methods

Study population

The patients originated from an ultrasonographic screening programme involving 65–75-year-old men in a defined geographical region during 1994–1997[25]. Over 4800 men participated in the programme and 191 had an anteroposterior aortic diameter of 30 mm or more. Patients with an AAA of 50 mm or more were referred for surgery. DNA containing blood samples were available from 77 men with an aneurysm between 3 and 5 cm who are currently followed by annual ultrasonographic imaging. Fifty-seven men who had been examined at least twice during the past 2–4·5 years were genotyped. Information on smoking habits was obtained by questionnaire.

Ultrasonographic measurements

Infrarenal aortic diameter was measured by B-mode imaging, using a Philips SDR 1550 scanner equipped with a linear 4-MHz transducer and a calliper light pen (Royal Philips Electronics, The Netherlands). All measurements were performed by an experienced ultrasonographer on a single apparatus. The results obtained by the two observers when both examined a group of 50 patients differed by less than 2 mm in 95 per cent of the patients[26].

Apolipoprotein E genotypes

Genotypes were determined by the polymerase chain reaction method of Hixson and Vernier[27] as described previously[28].

Statistical analysis

Differences between APOE genotypes in mean age, initial AAA diameter and observation time were tested using analysis of variance, and differences in the proportions of smokers were tested using a χ^2 test. The aneurysm expansion rate in each patient was estimated using the slope of the regression line of aortic diameter at time of examination. This method reduces the influence of measurement error compared with using only the first and last measurement of a series[29], but does not reflect the 'exponential growth' of the aneurysm in some patients. A multivariate regression model, with APOE genotype, smoking status, initial AAA diameter and age as independent variables, was used to test for the overall effect of APOE genotype on AAA expansion rate, to test for differences between genotypes (pairwise comparisons), and to calculate adjusted mean expansion rates with 95 per cent confidence intervals for the different APOE genotypes, as well as for smokers and non-smokers. Analyses were performed using SPSS version 9.0.0 (SPSS, Chicago, Illinois, USA).

Results

Table 1 shows the distribution of the patients by APOE genotype. Only four of the six possible genotypes were

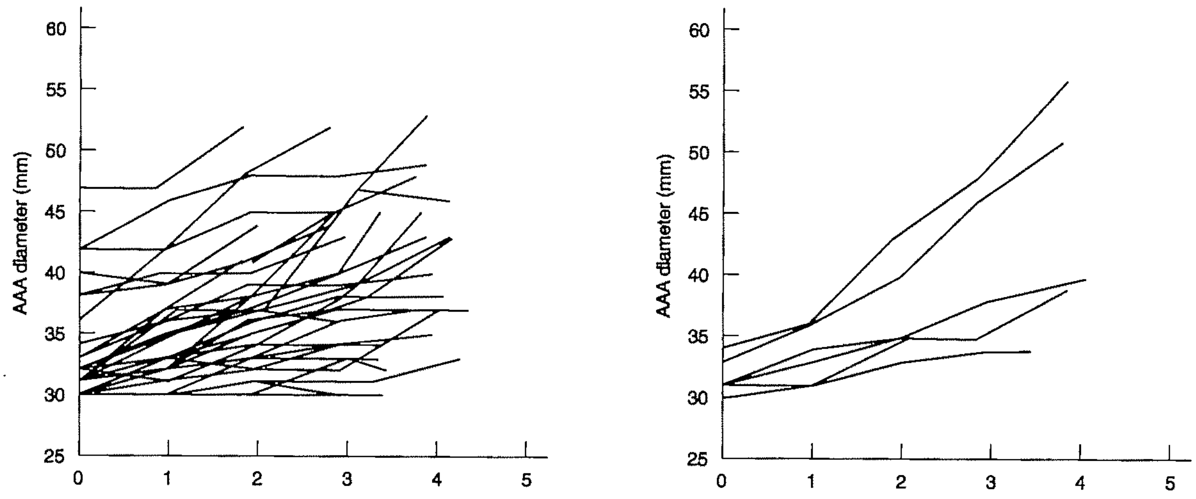
Table 1 Characteristics of men with a small abdominal aortic aneurysm (3–5 cm) and different apolipoprotein E genotypes

	APOE genotype				
Variable	E3E3 (*n*=31)	E3E4 (*n*=17)	E2E3 (*n*=6)	E2E4 (*n*=3)	*P*
Age (years)*	67·4(2·7)	67·8(2·9)	69·7(3·4)	67·3(4·0)	0·36
Initial diameter of AAA (mm)*	33·2(4·4)	32·2(2·5)	31·5(1·8)	33·3(2·5)	0·71
Observation time (years)*	3·6(0·7)	3·5(0·7)	3·6(0·8)	3·5(0·5)	0·95
Smokers†	17 (55)	12 (71)	3 (50)	2 (67)	0·70

*Values are mean(s.d.) ANOVA test; †values in parentheses are percentages (χ^2 test). APOE, apolipoprotein E; AAA, abdominal aortic aneurysm observed (i.e. no patients had genotype E2E2 or E4E4). The estimated allele frequencies are 0·079 (95 per cent confidence interval 0·039–0·149) for APOE*2, 0·746 (0·654–0·820) for APOE*3 and 0·175 (0·113–0·260) for APOE*4, which are similar to the frequencies estimated in two large Danish studies[30,31]. There were no significant differences between APOE genotypes with respect to age, AAA diameter at first examination and observation time or the proportion of smokers (*Table 1*).

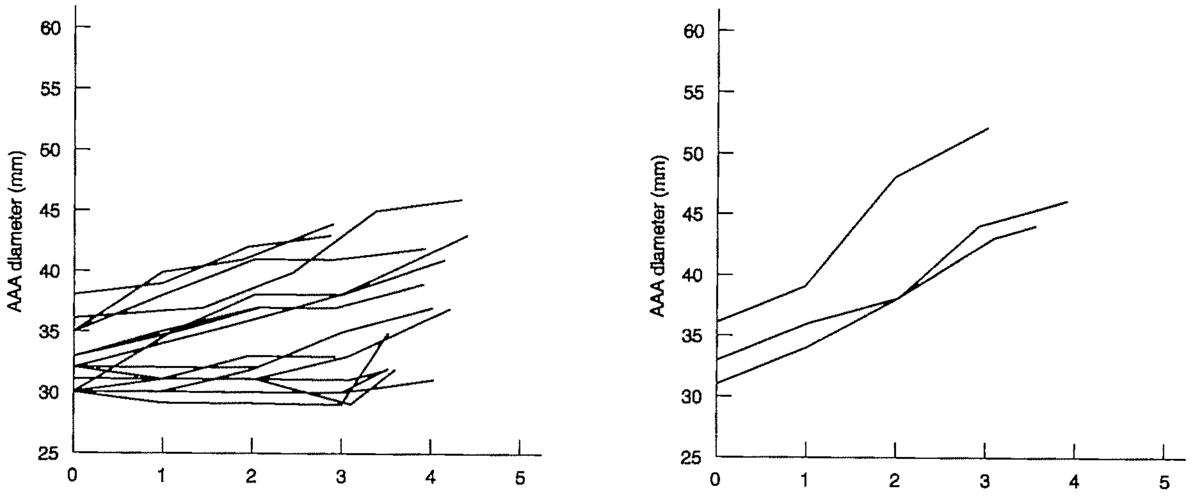
Fig. 1 shows the measured AAA diameters for all patients during follow-up. The aneurysms did not expand, or expanded less than 1 mm per year, in 11 patients (five with genotype E3E3 and six with genotype E3E4). On the other hand, six aneurysms expanded to more than 50 mm (three patients with genotype E3E3, two with genotype E2E3 and one with genotype E2E4).

Table 2 shows the mean AAA expansion rates in patients with the different APOE genotypes, adjusted for initial aortic diameter and smoking status (age had no effect and was excluded from the model). Overall, APOE genotype was a significant determinant of expansion rate ($P = 0{\cdot}001$). Compared with patients with genotype E3E3, those with



a E3E3

c E2E3



b E3E4

d E2E4

Fig. 1 Expansion of abdominal aortic aneurysms (AAAs) in patients with different apolipoprotein E genotypes

Table 2 Adjusted mean aneurysm expansion rate in each of the different apolipoprotein E genotypes

ApoE genotype	n	Expansion rate (mm/year)	P*
E3E3	31	2·1 (1·7–2·6)	—
E3E4	17	1·3 (0·7–1·9)	0·040
E2E3	6	3·1 (2·0–4·1)	0·102
E2E4	3	4·2 (2·7–5·6)	0·009

Values in parentheses are 95 per cent confidence intervals. The means were adjusted for initial abdominal aortic aneurysm diameter and smoking status. APOE, apolipoprotein E. *Pairwise comparison with genotype E3E3

E3E4 had a significantly lower AAA expansion rate, whereas the three patients with E2E4 had a higher rate. The expansion rates were not significantly different when all APOE*4 carriers (i.e. genotypes E3E4 and E2E4) were compared with patients with genotype E3E3 (P = 0·32), or with all patients without APOE*4 (i.e. genotypes E3E3 and E2E3; P = 0·19).

Smoking was independently and positively associated with aneurysm expansion. The mean rate in non-smokers was 2·2 (95 per cent confidence interval 1·5–2·8) mm/year compared with 3·0 (2·5–3·6) mm/year in smokers, adjusted for initial aortic diameter and APOE genotype (P = 0·014). Initial aortic diameter showed only a weak association with expansion rate after adjustment for smoking status and APOE genotype (P = 0·14).

Discussion

The present study suggests that the common polymorphism of the APOE gene is associated with differential expansion rates of small AAAs. Owing to small numbers, it is not possible to attach much importance to the results for the E2E3 (n = 6) and E2E4 (n = 3) genotypes, whereas the results for the two larger genetic subgroups (genotype E3E4 (n = 17) and E3E3 (n = 31)) are more substantial; they indicate that patients with E3E4 have a lower AAA expansion rate than E3E3 genotypes.

The opposite had been expected because subjects with E3E4 tend to have more atherosclerotic lesions in the abdominal aorta than subjects with E3E3[12–14]. It was assumed that aneurysms would expand faster in patients with more advanced atherosclerosis. APOE is, however, involved in several different biological processes[2,4] and thus may participate in pathogenic mechanisms unrelated to atherosclerosis. Furthermore, the AAA expansion rate may not simply be a function of the extent of aortic atherosclerosis, but may depend on other processes in the aortic wall[32,33].

The present study is small, and the results may have been influenced by selection bias. About one-third of the 191 men with an AAA larger than 30 mm identified in the screening programme either died or were referred for surgery before they completed at least two annual ultrasonographic examinations; the results could be biased if many of these 'lost patients' had the genotype E3E4. Another possible cause is that APOE*4 is associated with an increased cardiovascular mortality rate[34] and with Alzheimer's disease[35]. The association with Alzheimer's disease may also have caused APOE*4 carriers to be under-represented in the original AAA screening programme, and may have influenced the likelihood of APOE*4 carriers being offered surgical repair. It is reassuring, however, that the estimated APOE allele frequencies in the study are no different from the frequencies determined in two Danish population studies[30,31].

The use of linear regression will tend to underestimate the AAA expansion rate in some patients; notably in high and seemingly exponential expansion. However, these are few (*Fig. 1*) and cannot explain the observed differences in mean rates between APOE genotypes (*Table 2*). It was also considered whether the information obtained on smoking habits was too unreliable to permit sufficient control for confounding in the multivariate analysis. However, the information appeared valid because it was possible to show an effect of smoking on AAA expansion rate. Furthermore, the difference in the percentage of reported smokers between APOE genotypes was relatively small, so that possible information bias was unlikely to have had a substantial impact.

In conclusion, these preliminary findings suggest that the common polymorphism of the APOE gene is associated with differential expansion rates of small AAAs. Larger studies are clearly warranted.

Acknowledgements

The Danish Heart Foundation, The Foundation of Asta and Rosa Jensen, and the Health Department of Viborg County are thanked for financial support. The authors are indebted to Dr Lars Østergaard, Department of Infectious Diseases, Aarhus University Hospital, for valuable discussions and comments on the manuscript, and for organizing important laboratory work; and to Jonna Guldberg, Annette Stenderup, Gitte Glistrup Nielsen and Pia Hornbek for assistance in the laboratory.

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Clinical governance and the vascular surgeon

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Background: Audit of adverse outcome might allow identification of substandard surgical results. To test this hypothesis statistical modelling was applied to two indicator vascular procedures (elective abdominal aortic aneurysm repair and carotid endarterectomy) with accepted adverse event rates.

Methods: Binomial statistical models for varying adverse event rates were constructed. A power calculation was used in an attempt to predict the case numbers required to determine substandard results for individual surgeons and vascular units. Two scenarios were considered: first a base adverse event rate of 6 per cent and surgical practice with 9, 12 and 24 per cent morbidity rates, and second a base adverse event rate of 3 per cent and surgical practice with 6, 9 and 12 per cent morbidity rates.

Results: A mean of 57 elective abdominal aortic aneurysm repairs and 70 carotid endarterectomies were performed per annum. The adverse event rate for both operations was 4 per cent. Power calculations revealed that 130 patients would need to be studied to detect a surgeon with an adverse event rate twice 6 per cent and over 280 patients would be required with an adverse event rate twice 3 per cent. To gather this number of patients 2 years of unit data and between 3 and 22 years of individual data would need to be studied for a base adverse event rate of 6 per cent. A base rate of 3 per cent requires 7–47 years for an individual and 4–65 years for the unit. With a base adverse event rate of 6 per cent, detection of widely variant surgical practice (four times the morbidity rate as base) requires only 21 procedures.

Conclusion: Statistical modelling demands assumptions about accepted adverse event rates, confidence criteria and what constitutes substandard results. Data from large numbers of patients are required even for common operations with accepted adverse event rates. These data raise serious questions as to the feasibility of performing clinical governance on the basis of morbidity and mortality event rates alone.

Paper accepted 5 February 2000

British Journal of Surgery 2000, 87, 766–770

Introduction

The recent inquiry into the results of paediatric cardiac surgery in the UK has focused attention on maintaining acceptable standards of surgical outcomes. The reaction of the administrative bodies to a perceived inadequacy in maintaining standards has been to suggest clinical governance or 'audit with teeth'. Consultant surgeons will be appraised every 2 years[1]. Consultant physicians should be appraised annually[2]. It has been recommended that all doctors in the UK be required to prove competence[3]. There is, however, little information as to the exact process of this audit and its feasibility.

Humphreys[4], a vascular surgeon, drew attention to the problems of attempting wide ranging audit. Patient selection, individual *versus* unit audit, and the mechanics of the audit procedure are all confounding variables preventing accurate and just assessment of surgical outcome. Even more central questions include whether surgeons can perform this audit, whether there exist agreed standards of care and at what level is care substandard.

In vascular surgery there are two indicator procedures: elective abdominal aortic aneurysm (AAA) repair and carotid endarterectomy (CEA) for which agreed adverse event rates exist from level 1 (randomized) data. The generally accepted mortality rate for elective AAA repair ranges from 5 to 6 per cent. The most recent data come from the UK Small Aneurysm Trial[5] in which a mortality rate of 5·8 per cent was reported[5]. The indicator adverse event rate for CEA is the combined stroke and death rate. The adverse event rate for CEA varies between 3 and 10 per cent but two major multicentre trials, the North American Symptomatic

Carotid Endarterectomy Trial (NASCET)[6] and European Carotid Surgery Trial (ECST)[7], described combined mortality and stroke rates of 5·8 and 6·0 per cent respectively. It seems acceptable from the standpoint of statistical modelling to assume an adverse event rate of 6 per cent for both of these procedures. However, the recent Asymptomatic Carotid Atherosclerosis Study[8] has reported a lower adverse event rate of 3·2 per cent. It has been argued that the NASCET and ECST studies are outdated and that a 3 per cent adverse event rate for carotid surgery in asymptomatic patients is current best surgical practice.

The aim of this study was to use these two indicator procedures to produce a statistical model that could help perform clinical governance. The study identified what type of statistical parameters would need to be set, how much data might need to be collected and over what time interval.

Materials and methods

To be secure in a judgement of poor practice it must be ensured that the observed experience is inconsistent with normal acceptable practice and also that it is truly indicative of poorer performance.

A widely used and accepted method of predicting the number of events that would need to be studied to identify a difference between two groups is a power calculation[9]. In the present application, it is assumed that the acceptable surgical adverse event rate is a particular number (e.g. 6 per cent). The observed number of adverse events that occur in a given number of surgical procedures is investigated. It is quite possible in a sample of 100 procedures for adverse events to occur in 9 per cent, when in fact the genuine base rate is only 6 per cent; this outcome has a 15 per cent probability (the binomial probability of nine or more adverse events in 100 procedures when $P = 0{\cdot}06$ is 0·15). It is assumed that adverse events are random, independent occurrences imposed on a fixed underlying rate. The term 'base rate' is used to represent the accepted adverse event rate (e.g. 6 per cent). The term 'alternative rate' denotes a higher rate of adverse events, which may reflect surgical outcomes requiring attention. In the present analysis, base rates of 3 and 6 per cent were considered separately.

An observed or sampled rate of adverse events of 9 per cent may not be inconsistent with a true underlying base rate of 6 per cent, as demonstrated above. The question of how high an observed rate needs to be to be deemed inconsistent needs to be addressed. The conventional statistical answer is to adopt a criterion of 'rarity' of 0·05. That is, in observing 100 procedures, when an adverse event base rate of 6 per cent applies, the probability of 11 or more adverse events happens to be 0·038, which is rare, being less than the criterion. It should be noted that such an outcome will occur 4 per cent of the time when the base event rate really is 6 per cent. This reasoning rests on the premise that the adverse event base rate of 6 per cent is true.

This is not enough to conclude that the observed adverse event rate (11 of 100) truly reflects a rate higher than 6 per cent. Alternatively if an underlying adverse event base rate of 9 per cent is assumed the probability of 11 or more adverse events is 29 per cent. This is not the 95 per cent level required of chance and is hardly enough to feel confident that 9 per cent is the true underlying rate. This probability, of extreme observations under the alternative rate, is referred to as 'power'. In summary, if the adverse event base rate of 6 per cent is accepted and the criterion of rarity of 5 per cent is used, observations falling out of this range are unlikely or inconsistent with that base rate. In addition, requiring a power of 95 per cent ensures that such observations are quite consistent with the alternative adverse event base rate proposed (9 per cent). Statistical convention usually (but not always) adopts asymmetric criteria for rarity and power, 5 and 80 per cent respectively. To make the arguments conservative, the present analysis adopted a power criterion of only 80 per cent.

The choice remained of which base and alternative adverse event base rates reflecting standard and substandard practice should be used in this study. For a base adverse event rate of 6 per cent three scenarios have been examined, alternative adverse event rates of 9, 12 and 24 per cent. For a base rate of 3 per cent, the alternative rates chosen were 6, 9 and 12 per cent. Under these circumstances, using a criterion of rarity of 5 per cent and requiring power of 80 per cent, the number of procedures required to identify substandard surgical practice was investigated.

Review of prospectively collated data from a typical urban vascular unit spanning 9 years (1989–1997) allowed identification of the time required to supply the number of cases predicted by the power calculation. The data were stored on a vascular database that was collated from theatre records and patient notes prospectively by a single data manager and audited monthly to ensure data capture.

Results

Table 1 shows, for various combinations of base and alternative adverse event rates, the number of operations required to achieve a criterion of rarity less than or equal to 0·05, while ensuring that the power was as close to 80 per cent as possible without exceeding it. The binomial distribution for the rates chosen does not yield exact probabilities, so the results are presented for a criterion of rarity as near as possible to 0·05. Power was determined conservatively: the smallest number of operations required to achieve power in excess of 80 per cent was first

Table 1 Power, error rate and number of operations required to detect abnormal outcomes under varying alternative event rates

	Alternative rate (%)			
	6	9	12	24
Adverse event base rate 6 per cent				
Error rate*	—	0·048	0·049	0·034
Power	—	0·798	0·796	0·779
No. of adverse events†	—	37	13	4
No. of operations‡	—	463	130	21
Adverse event base rate 3 per cent				
Error rate*	0·046	0·045	0·042	—
Power	0·798	0·797	0·790	—
No. of adverse events†	14	6	4	—
No. of operations‡	281	86	44	—

*Error rate chosen to be less than or equal to 0·05; †minimum number of adverse events required to be confident that alternative rate (or higher) is the true rate; ‡smallest number of operations such that power is closest to 0·80 without exceeding it

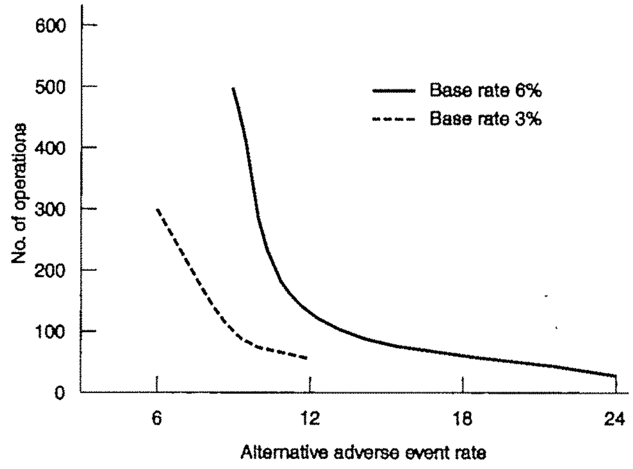

Fig. 1 Effect of increasing adverse event rates on the number of patients required to prove alternative adverse event rates

determined; then, among smaller numbers, the one with largest power (of necessity less than or equal to 80 per cent) was selected.

For a base rate of 6 per cent, detecting an adverse event rate of 9 per cent requires 463 patients to be studied. An observed adverse event rate of at least 37 (8 per cent) of 463 is then required to be confident that such an outcome is rare (0·048) under the base rate and simultaneously typical (0·798) of the alternative rate. An adverse event rate of 12 per cent requires 130 patients. Even an adverse event rate four times the base rate (24 per cent) requires 21 or more procedures to be studied (*Fig. 1*). For a base adverse event rate of 3 per cent, over 280 patients would need to be studied to detect a true adverse event rate twice base (6 per cent).

The results for elective AAA repair and CEA in this unit between 1989 and 1997 are shown in *Table 2*. The letters A–E denote individual surgeons. Surgeon A did not perform any carotid surgery in this period.

There was a wide range of activity (operations per annum) and results. For elective aneurysm repair surgeons C and E had the highest activity, yet widely different adverse event rates. Surgeons A, B and D had similar, but lower activity rates but also widely varying adverse event rates. This lack of correlation between activity and outcome was also seen in the CEA figures.

Table 2 also shows the time it would take to accumulate the number of operations predicted to be required by the power calculation under these different scenarios. With a base rate of 6 per cent and an adverse event rate of 12 per cent (double the base rate), the unit as a whole would need to collect between 2 years of data for either CEA or elective AAA repair. For an individual surgeon it ranged between 3 and 22 years. When the adverse event base rate is lowered to 3 per cent and the adverse event rate is 6 per cent (again double the base rate), the unit needs to collect data for 5 years, and an individual up to 47 years. When extreme practice was considered, an adverse event base rate of 6 per cent and an adverse event rate of 24 per cent, the unit would need to study 21 operations, taking just over 4 months for AAA repair and 3 months for CEA. The variation for an individual surgeon was wider, from 6 months to just over 3 years.

Discussion

Substandard outcome from surgery is undesirable but substandard surgical practice is undefined. Advocates of evidence-based medicine would suggest that evidence from randomized level 1 trials should form the basis of acceptable adverse event rates. This information is not always available

Table 2 Activity, adverse event rates and number of operations required to predict an adverse event rate twice the base rate (130 for 6 per cent base rate, 280 for 3 per cent base rate) for the unit and individual surgeons (1989–1997)

	No. of operations	Time interval (years)	Mean no. per year	No. of adverse events	Time to 130 operations (years)	Time to 280 operations (years)
Elective abdominal aortic aneurysm repair						
Surgeon A	68	5	14	3 (4)	9	20
Surgeon B	53	9	6	0 (0)	22	47
Surgeon C	180	9	20	10 (6)	6	14
Surgeon D	47	6	8	2 (4)	16	35
Surgeon E	161	9	18	4 (2)	7	15
Unit	512	9	57	19 (4)	2	5
Carotid endarterectomy						
Surgeon B	55	9	6	4 (7)	22	45
Surgeon C	148	9	16	11 (7)	11	17
Surgeon D	61	6	10	0 (0)	13	28
Surgeon E	363	9	40	12 (3)	3	7
Unit	627	9	70	27 (4)	2	4

Values in parentheses are percentages

and publication bias may make these levels unachievable everywhere. A base adverse event rate of 6 per cent was used here and is in tune with the evidence. The application of this base rate to all individuals, all vascular units, all countries and all health care systems is not possible. Adverse event rates of 0·01 per cent in the aviation industry equate to two unsafe plane landings per day at Chicago's O'Hare airport[10]. Costly 'fail safes' that exist in the aviation industry such as buffering, system automation and redundancy are missing in medical practice[10]. Expectations concerning error reduction will continue but are unlikely to be realized until the real cost of high-quality medical care is recognized.

Audit has been promoted as a reliable method of performing quality control. For audit to be meaningful, surgical procedures should be audited not just by audit clerks or administrators, but by clinicians. The team-orientated approach that exists in other industries should be adopted and anaesthetic staff, intensive care staff, nurses and other clinical support groups should be included. This would improve communication and prevent practice in isolation. Audit of outcome requires reliable data collection, data entry and identification of reproducible outcome indicators over and above morbidity or mortality rates. Comparative data must be available to know whether current practice is acceptable. Patient selection is an uncontrolled variable that may have greater influence on outcome than the surgeon or the surgical procedure[11]. Rothwell *et al.*[12] used the ECST database to demonstrate how unacceptable surgical practice may simply be the result of variable case mix. For these very reasons crude mortality figures, as presented here, are not enough. The Vascular Surgical Society of Great Britain and Ireland has turned its attention to Physiological and Operative Severity Score for enUmeration of Mortality and morbidity (POSSUM) scoring[13]. POSSUM scoring, or even just the physiology score component, may allow comparison between individuals and units[13]. Recent correspondence has, however, highlighted difficulties in interpretation of POSSUM scoring; clearly even POSSUM scoring can be manipulated to best surgical advantage[14].

When should the clinical monitoring system warn of a problem? Three scenarios related to two different base event rates were outlined in this paper for illustration. A power calculation relating to these scenarios has been performed, assuming that adverse events occur as independent binomial trials. The convention of 'acceptable practice' has also been used when performing the calculation. For a base adverse event rate of 6 per cent, to identify widely variant outcomes of four times the accepted practice would require the study of 21 procedures. However, to determine that one surgeon's outcome was 50 per cent worse than another's might require the study of more than 20 years of work. While the statistical model used to illustrate this point is an oversimplification, the long intervals required to gather information are none the less sobering. A rolling 5-year unit audit could help to smooth out this problem. The relevant adverse event rates for the previous 5 years would be averaged. The following year the most recent year's figures would be added and the data from 6 years previously discarded. This may allow for the examination of a trend and help to eliminate rash conclusions from the clustering of adverse events noted by Humphreys[4].

There is a wide range of clinical activity between surgeons; in this study activity was not related to adverse event rates. The generation of individual figures presents a dilemma both for the head of the unit and the individual surgeon. Should the unit head seek to retrain surgeons C and B as their CEA adverse event rate was greater than 7 per cent? These event rates were twice those of surgeon E yet no different from published values. Informed consent is also at issue. Which adverse event rate should a surgeon quote to a patient? The Bristol case highlighted the inadequacy of quoting a national outcome rate that did not reflect local practice.

This statistical model has demonstrated that crude surgical mortality rates are not an adequate tool for clinical governance. Accepted surgical practice needs to be defined and it may be that surgical scoring systems will allow comparison of like with like.

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Vascular Surgical Society

Use of superficial femoropopliteal vein for suprainguinal arterial reconstruction in the presence of infection

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Background: Conventional treatment of mycotic aneurysms or graft infections of the aortoiliac segment by *in situ* or extra-anatomic prosthetic reconstruction has a high mortality and morbidity rate, with a substantial risk of persistent graft infection. The use of autologous vein may reduce this.

Methods: Eleven patients with suprainguinal arterial infections including two with mycotic aortic aneurysms, four with aortic graft infections, four infected femorofemoral grafts and an infected axillofemoral graft were treated by debridement and *in situ* reconstruction with autologous superficial femoropopliteal vein. All patients received appropriate antibiotic therapy and were followed by regular postoperative duplex imaging. Preoperative femoral vein duplex imaging was performed in eight of the 11 patients.

Results: Ten of the 11 patients survived with a functioning graft and without limb loss or evidence of infection at 4–33 months. One patient died from myocardial infarction after operation. Three patients had minor swelling of one leg. Four patients required subsequent angioplasty of anastomotic stenoses detected by duplex surveillance.

Conclusion: Superficial femoropopliteal vein is an excellent conduit for suprainguinal reconstruction in the presence of infection. Duplex imaging is useful for confirming the suitability of deep veins for use as a graft and for postoperative surveillance.

Paper accepted 5 February 2000

British Journal of Surgery 2000, 87, 771–776

Introduction

Infection is one of the most feared complications in vascular surgery, especially when it involves the aortoiliac segment. Prosthetic graft infections in this region are associated with a high mortality rate (10–25 per cent), a considerable risk of limb loss (10–25 per cent) and a high incidence of reinfection of any new prosthetic graft (10–25 per cent)[1–3]. Mycotic aneurysms of the aorta and iliac arteries are also associated with a high mortality rate (25 per cent) and a similar high risk of infection of any prosthetic graft used to reconstruct the affected artery[3–7].

Once graft infection is established, antibiotic therapy alone is unlikely to be adequate treatment[2,7]. Graft excision is required to prevent anastomotic disruption and graft–enteric fistulas, which increase the mortality rate to about 50 per cent[2,3,8]. Whereas simple graft excision may be used occasionally, this will give rise to severe lower limb ischaemia in most patients with, at best, major limb amputations and in many cases gluteal ischaemia and death. Thus, arterial reconstruction is often indicated but the way in which this can be accomplished is controversial.

The standard approach is to excise the infected graft or infected arterial wall and to oversew the aortic stump, performing a prior or subsequent extra-anatomic reconstruction such as an axillofemoral graft in an uninfected field. However, this may not always be possible (e.g. in the case of an infected aortobiprofunda graft). When it can be done, it is a major undertaking with a risk of aortic stump disruption and infection of the new graft[1–9]. *In situ* reconstruction with an antibiotic-bonded prosthesis is gaining popularity[3,10] and this may give a reasonable chance of clearing chronic low-grade graft infections due to *Staphylococcus epidermidis*. However, it is less likely to meet with success in acute infections, such as with *Staphylococcus aureus*, *Pseudomonas* or coliforms, particularly when frank pus is present[1,10].

Other alternatives include the use of autologous tissue, such as long saphenous vein[11–13], endarterectomized native vessels and superficial femoral arteries[14], or arterial allografts[15]. Autologous superficial femoropopliteal vein (SFPV) has been used with success by Clagett *et al.*[16–18] and Nevelsteen *et al.*[19,20] as well as others[11,21–23]. This paper describes an experience of the use of femoropopliteal veins for arterial reconstruction in 11 patients with suprainguinal prosthetic or arterial infection.

Patients and methods

Eleven patients aged 56–85 years (eight men and three women) presented over a 3-year interval with a mycotic aortic aneurysm (two patients) or suprainguinal prosthetic graft infection (nine). The patients' characteristics are described in *Table 1*. The two mycotic aneurysms grew *Streptococcus* group A and methicillin-resistant *S. aureus*. The nine prosthetic graft infections involved an aortobifemoral graft in three patients, one aortic tube graft, one axillofemoral graft and four femorofemoral grafts. The patients presented with infection between 12 days and 5 years after the original operation. One patient had undergone a previous replacement of a chronically infected femorofemoral graft with a rifampicin-bonded graft, which had become reinfected. Coliforms were the responsible organism in two aortic and one femorofemoral graft infection and *Serratia* was responsible for one aortobifemoral infection. No pathogen was isolated in the remainder despite the presence of pus around the prosthesis and the absence of graft incorporation into the surrounding tissue. *S. epidermidis* infection was suspected in three patients as they had chronic infections occurring 1–5 years after the original operation and there was a characteristic slime around the graft.

Graft infection was diagnosed in all patients by the presence of fluid around the graft on preoperative computed tomography (CT) or ultrasonography and by the lack of incorporation of the graft by the tissues at operation. In eight of nine patients a preoperative diagnosis was made by the aspiration of pus from the perigraft fluid. The preoperative diagnosis of mycotic aortic aneurysm was made on the basis of CT, a high fever and leucocytosis and, in one patient, positive blood cultures.

Preoperative duplex imaging was performed in eight of the 11 patients to confirm the suitability of the SFPV as a graft. In two this showed the SFPV to be inadequate on one side. In a further patient, not included in this series, the femoral veins were both found to be unsuitable for use as a

Table 1 Presentation and diagnosis of patients with mycotic aneurysms or infected grafts

Patient	Age (years)	Sex	Diagnosis	Organism	Previous surgery
1	56	M	Infrarenal mycotic aortic aneurysm	Group A *Streptococcus*	None
2	67	M	Infrarenal mycotic aortic aneurysm	MRSA	Transurethral prostatectomy 6 weeks previously
3	62	M	Infected aortobiprofunda Dacron graft	*Serratia*	Aortic aneurysm repair (tube graft 28 days previously converted to aortobifemoral for thrombosis 1 day after operation)
4	66	M	Infected aortoiliac Dacron graft	Coliform	Aortoiliac graft for aortic aneurysm 12 days previously
5	60	F	Infected aortobifemoral Dacron graft	Coliform	Aortobifemoral graft 14 days previously for aortic occlusion with severe claudication
6	56	M	Infected right limb of aortobifemoral Dacron graft	No organism grown (?*Staphylococcus epidermidis*)	Emergency aortobifemoral graft and bilateral femoropopliteal vein bypasses for acute aortic occlusion 5 years previously
7	85	M	Infected femorofemoral crossover Dacron graft	Coliform	Femorofemoral and left femoropopliteal (PTFE) graft 3·5 years previously
8	72	F	Infected femorofemoral Dacron graft and left rest pain with femoropopliteal occlusion	No organism grown (?*Staphylococcus epidermidis*)	Femorofemoral graft 5 years previously replaced with *in situ* rifampicin-bonded Dacron graft 1 year previously
9	62	M	Infected femorofemoral crossover Dacron graft	No organism grown (?*Staphylococcus epidermidis*)	Femorofemoral graft 14 months previously for claudication
10	61	M	Infected femorofemoral Dacron graft and left rest pain with femoropopliteal occlusion	No organism grown	Femorofemoral graft 6 weeks previously for critical ischaemia
11	73	F	Infected axillofemoral Dacron graft	No organism grown	Axillofemoral graft 3 weeks previously for rest pain

MRSA, methicillin-resistant *Staphylococcus aureus*; PTFE, polytetrafluoroethylene graft, necessitating the use of endarterectomized superficial femoral artery. In patient 10 the presence of an infected femorofemoral graft was found at operation for a secondary femorodistal bypass.

Surgical technique

All 11 patients were treated by SFPV reconstruction. Initially, the SFPV was dissected out, dividing the branches between clips as far as the knee joint (*Fig. 1*). For aortobifemoral reconstruction (patients 3 and 5) vein was harvested from both legs whereas a single vein sufficed for aortoiliac, iliofemoral or femorofemoral reconstruction. The infected graft or mycotic aneurysm was then exposed. For the aortic reoperations a midline abdominal incision was used, but a left 11th rib extraperitoneal approach was used in patient 5 as this had been the original approach for the aortobifemoral graft 2 weeks earlier. After securing arterial control the graft or mycotic aneurysm was excised with careful debridement of all infected tissue, washing the infected area with povidone–iodine solution. The SFPV was then removed, ligating and dividing it just beyond the profunda femoris vein, and at, or just below, the knee joint. In this way, 30–35 cm of good quality vein was usually obtained from each leg. The graft was then inserted (*Fig. 2a* and *b*) in standard fashion.

The various graft configurations used for reconstruction are summarized in *Fig. 3*. In patient 1 the SFPV was bifurcated and was used in the antegrade fashion as a trouser-type aortoiliac graft (*Fig. 2a* and *b*). In two patients (2 and 4) the reconstruction comprised a non-reversed aortouni-iliac SFPV graft with a further reversed vein graft to the opposite iliac artery from the body of the graft. The valves in these grafts were disrupted using a Karmody valvulotome with the top clamp released after completion of the aortic anastomosis. This configuration ensured a larger calibre graft at the end-to-end aortic anastomosis. In all other operations reversed vein reconstructions were employed. In patient 3 an aortounifemoral plus femorofemoral graft was used because of a shortage of femoral vein of adequate calibre, whereas a new trouser graft was fashioned from SFPV in patient 5. Patient 6, who presented with a groin abscess 5 years after an emergency aortobifemoral graft for an aortic occlusion, had an infection that appeared to be limited to a single limb of the graft, which was replaced with reversed SFPV. In the remaining five patients reversed SFPV was used for femorofemoral grafts in four and an iliofemoral graft in one (to replace an infected axillofemoral graft). In two patients (8 and 10) a reversed SFPV femorofemoral graft was combined with a reversed vein femorodistal bypass for critical ischaemia.

Intra-abdominal grafts were wrapped in greater omentum and the area was packed with gentamicin-impregnated

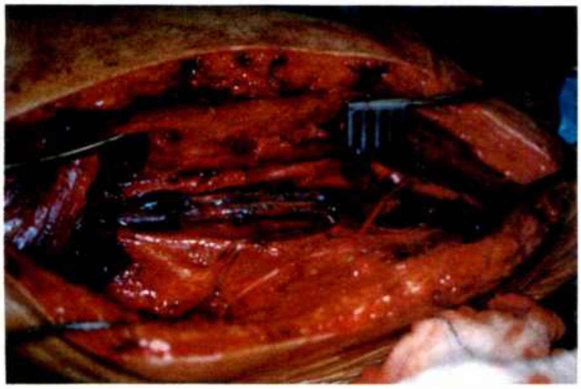


Fig. 1 Exposure of the superficial femoral vein (patient 1)

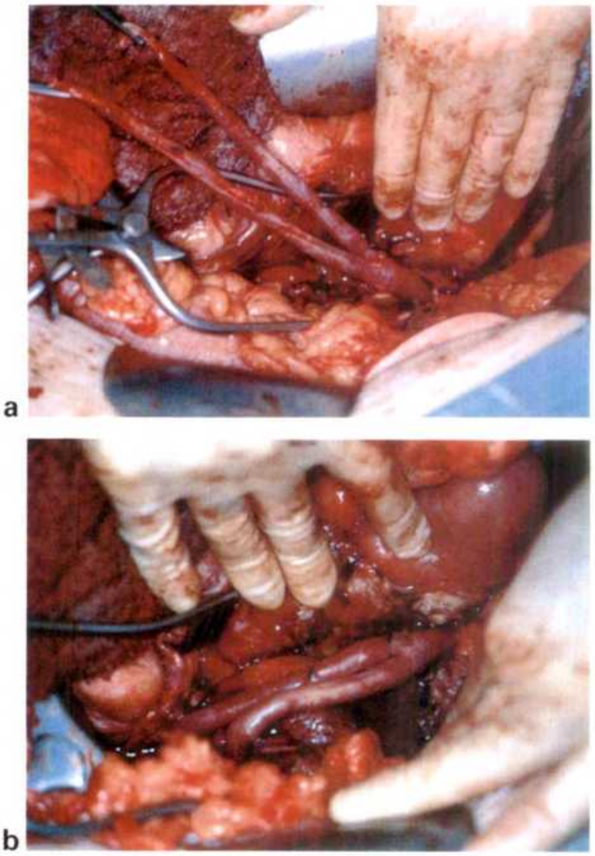
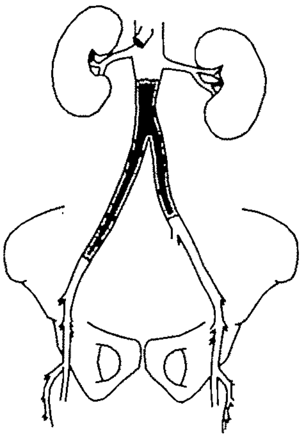


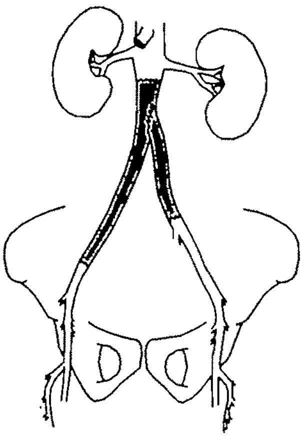
Fig. 2 Stages in the operation (patient 1; mycotic aortic aneurysm).

a Insertion of the bifurcated femoral vein.

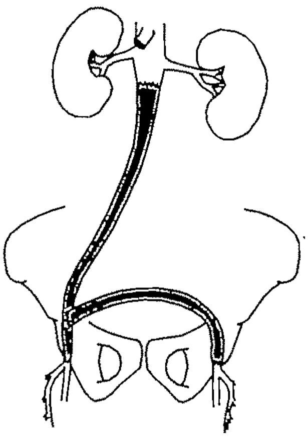
b Finished graft after valve disruption and completion of the lower anastomosis



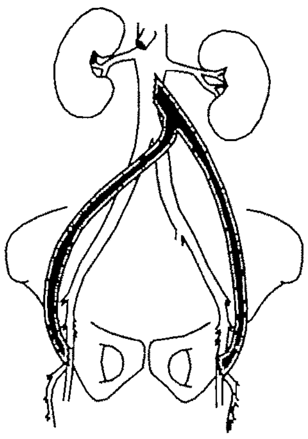
Patient 1
Bifurcated single
SFPV



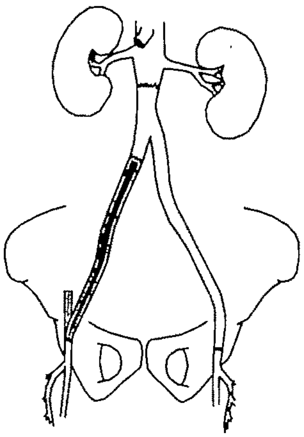
Patients 2 and 4
Composite antegrade and
retrograde single SFPV



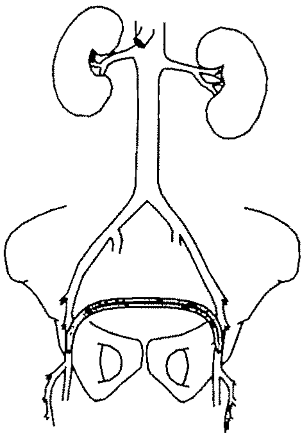
Patient 3
Reversed SFPV,
two veins



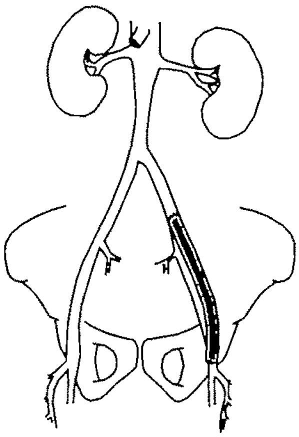
Patient 5
Reversed SFPV,
two veins



Patient 6
Reversed
SFPV



Patients 7–10
Reversed
SFPV



Patient 11
Reversed
SFPV

collagen foam or gentamicin beads. Multiple suction drains were used after operation. Antibiotic cover with co-amoxiclav, gentamicin, teicoplanin and metronidazole was started before operation and continued for 5 days, with subsequent modification according to bacteriological sensitivities. In most patients oral antibiotics were continued for 6 weeks.

The grafts were imaged using duplex Doppler ultrasonography at 6 weeks and subsequent 3-month intervals for 1 year, and then every 6 months for the next 2 years. Stenoses greater than 70 per cent were treated by percutaneous angioplasty under angiographic control.

Results

One patient, who had a history of myocardial ischaemia, died in the immediate postoperative period, following a cardiac arrest 1 h after surgery. The remaining patients all recovered well and are alive at 4–33 months. One patient had a minor groin wound infection. To date, no patient has had a recurrent infection, all grafts remain patent and there have been no major limb amputations.

In most patients postoperative duplex Doppler imaging showed a satisfactory graft. In patient 2 a mild (50 per cent) stenosis at the venovenous anastomosis prompted intra-

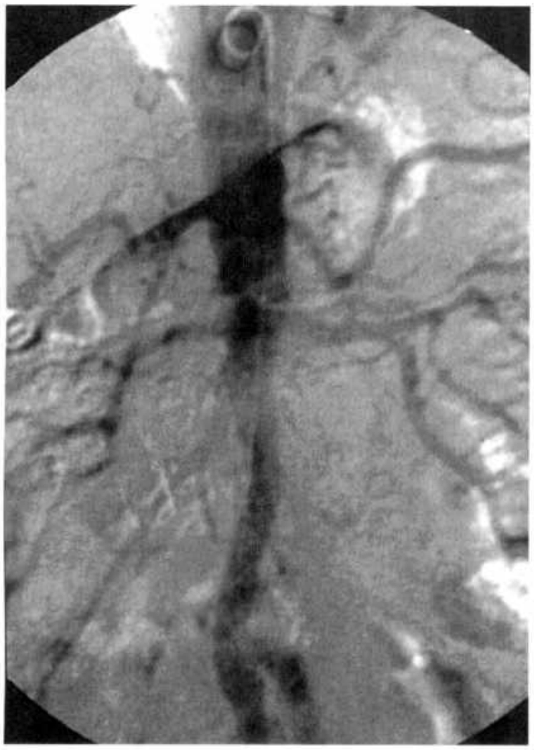


Fig. 4 Intra-arterial digital subtraction angiogram of the completed graft at 6 weeks (patient 2)

arterial digital subtraction angiography that showed a satisfactory graft (*Fig. 4*). Four patients developed a significant anastomotic stenosis (greater than 70 per cent), identified on duplex imaging within 6 months. The aortic anastomosis in patient 3, and the profunda anastomosis of patients 6 and 10, underwent successful angioplasty with good angiographic results confirmed on duplex imaging. In one the angioplasty was successfully repeated 3 months later for a restenosis. In patient 9, a 70 per cent stenosis was found at 6 weeks in the donor vessel above the femorofemoral graft and was dilated percutaneously with some improvement. Angioplasty was repeated at 9 months, again with moderate results.

Three patients developed mild oedema of donor legs after operation which had completely resolved at 12 months in one. Neither of the two patients whose long saphenous veins had been removed previously from the donor leg developed significant limb oedema.

Discussion

Eleven patients with suprainguinal arterial or graft infections treated by excision, debridement, *in situ* reconstruction with superficial femoral vein and antibiotics are reported here. Ten patients survived with complete eradication of infection and without limb loss. These results accord with those reported by Clagett *et al.*[17] and Nevelsteen *et al.*[19] using the same technique with a mortality rate of about 10 per cent and limb loss rate of 5 per cent. Recently, Gordon *et al.*[18] described a subgroup of patients with particularly difficult graft infections treated with this technique, including many who had already undergone multiple unsuccessful procedures or who had open groin wounds or graft–enteric fistulas. They reported four deaths and four amputations in 17 patients, as might be expected in these difficult cases. Secondary anastomotic haemorrhage was seen in one of their patients. There was none in the present series although lower risk patients were included. Secondary haemorrhage might be more common from saphenous or arm vein; femoral and popliteal veins may be more resistant to infection as they have somewhat thicker walls, despite the fears of some authors[10].

While the pioneering work on this technique is attributable to Clagett and Nevelsteen, superficial femoral veins had previously been used extensively by Schulman *et al.*[24] for femoropopliteal bypass. There have also been occasional case reports using saphenous vein reconstruction after removal of infected aortic grafts[11–13]. Two other groups have reported small series of SFPV grafts for aortoiliac reconstruction in infected fields with similarly encouraging results[21–23]. Limb swelling and venous insufficiency have been surprisingly rare both in the present experience and that of others[16–19,25]. Similarly, fears of late aneurysm formation do not appear to have been realized in up to 5 years' follow-up[17,20,25]. The overall mortality rate in the 99 patients reported to have had SFPV reconstruction for infection to date is 12 per cent with a 7 per cent rate of limb loss, which compares favourably with more conventional treatment[3–7].

The operation can be long and technically demanding. More recently in the authors' unit two surgeons have been employed, working simultaneously. The femoropopliteal vein dissection can take up to 1 h, so if veins from two legs are required these can be harvested simultaneously. Alternatively, if only one vein is required, this can be harvested while the aorta is exposed. The periaortic tissues surrounding an infected graft or a mycotic aneurysm are often fibrotic and inflamed making this part of the operation very challenging. The reconstruction is generally straightforward but care must be taken to equalize the diameters of the venous and aortic orifices for end-to end anastomoses. Spatulation of the vein tends to cause angulation and probably resulted in the anastomotic stenosis in patient 3 which required angioplasty at 6 weeks. Bivalving the vein by making two longitudinal slits 1–2 cm long on opposite sides of the vein allows a more symmetrical anastomosis without angulation and may reduce the risk of anastomotic stenosis. In some cases the femoral end of the vein is of larger calibre. In these instances an antegrade configuration with valve disruption gives a better equalization of diameters for end-to-end aortic anastomosis.

Duplex imaging is valuable for planning surgery by confirming the suitability of the femoral–popliteal vein complex for use as a conduit. In some patients the femoral vein may be too small for aortic replacement whereas others may have suffered a previous deep vein thrombosis in a prolonged illness, especially if multiple procedures have already been performed. Duplex ultrasonography is also useful for postoperative surveillance; four patients in this series developed an anastomotic stenosis that required angioplasty.

While the present series is relatively small, it provides valuable support for the work of Clagett and Nevelsteen which has yet to gain full acceptance[10]. Suitable femoral and popliteal veins are available in most patients and appear to give results superior to those of other methods for the treatment of suprainguinal graft infection or mycotic aneurysms.

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Randomized clinical trial of the effect of needle gauge and local anaesthetic on the pain of breast fine-needle aspiration cytology

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Background: Breast fine-needle aspiration cytology (FNAC) is an invasive investigation which can be uncomfortable or distressing. This randomized study investigated the discomfort of breast FNAC and the effect of different techniques.

Methods: Some 116 FNAC samples were taken from 98 women with a palpable breast mass. Each patient was randomized to one of four study groups; aspiration was performed using a green-hub (21 G) or blue-hub (23 G) needle, either with or without local anaesthetic. Each patient scored the pain of the whole procedure using a visual analogue scale.

Results: A green-hub needle caused significantly more discomfort (mean(s.e.m.) pain score 5·1(0·4) cm) than a blue-hub needle (2·9(0·4) cm), or either a blue- or green-hub needle with local anaesthetic (3·0(0·4) and 2·1(0·4) cm respectively) ($F = 10{\cdot}28$, 3112 d.f., $P < 0{\cdot}01$, analysis of variance).

Conclusion: The discomfort of breast FNAC is dependent upon the gauge of the needle and the use of local anaesthetic. A blue-hub needle without local anaesthetic should be first choice for breast FNAC.

Presented in part to the British Association of Surgical Oncology, Aberdeen, UK, July 1997 and to the Fifth International Breast Cancer Conference, Nottingham, UK, September 1997, and published in abstract form as *Eur J Surg Oncol* 1997; 23: 376 and *Breast* 1997; 6: 252

Paper accepted 27 November 1999

British Journal of Surgery 2000, 87, 777–779

Introduction

Fine-needle aspiration cytology (FNAC) is well established in the assessment of a palpable breast mass[1–3]. A green-hub (21 G) needle is often recommended for breast FNAC as it is thought to provide more cellular samples[4]. The diagnostic accuracy of breast FNAC, however, appears to be independent of needle size and the use of local anaesthetic[5,6]. It is often assumed that FNAC of the breast is no more painful than venepuncture and that it is only the moment of skin puncture that is painful[7,8]. This was a randomized prospective study of the level of discomfort experienced by patients undergoing FNAC to determine whether pain was influenced by the gauge of needle used or the presence of local anaesthetic.

Patients and methods

The study included consecutive women presenting to the breast clinic with a palpable breast mass. Each patient was randomized (using random number sheets) to one of four study groups and aspiration was performed using either a blue-hub (23 G, 0·6 × 30 mm) or green-hub (21 G, 0·8 × 40 mm) needle, with or without local anaesthetic. Informed consent was obtained before each FNAC procedure.

All aspirates were obtained, by the two authors, using a standard technique of ten passes of the FNAC needle through the lesion[5]. Patients randomized to receive local anaesthetic had 2 ml of 1 per cent lignocaine infiltrated beneath the skin and along the intended path of the FNAC using a blue-hub needle. The lignocaine was left *in situ* for 3 min before the FNAC procedure. Women found to have a simple cyst upon FNAC were excluded from the study.

The pain of the whole procedure, including the infiltration of local anaesthetic, was assessed by means of a 10-cm horizontal linear visual analogue scale[9], ranging from no pain at 0 cm to agonizing pain at 10 cm[10]. Each patient marked the scale, at a point corresponding to the discomfort experienced within 5 min of the aspiration, before the end of the consultation.

Statistical analysis

The difference in mean pain scores between study groups was assessed using one-way analysis of variance (ANOVA) and the two-sample *t* test as appropriate[11]. As no previous data existed regarding the pain of breast FNAC, the sample size for the study was calculated from an ongoing analysis of the mean pain scores. Twenty-three FNAC samples per group were required to give a 90 per cent probability of detecting a 2-cm difference in mean pain scores (blue-hub *versus* green-hub needle, no local anaesthetic) at the 5 per cent significance level. The data were analysed using SPSS software (SPSS version 7.0; SPSS, Chicago, Illinois, USA).

Results

A total of 116 FNAC samples were taken from 98 women with 104 palpable solid tumours. Twelve patients found to have a breast cyst were excluded from the study. Twenty-five of the samples were taken from malignant breast tumours. A comparison of the mean pain scores is shown in *Table 1*. There was a significant difference in the level of pain experienced between the four study groups. The greatest discomfort (mean(s.e.m.) pain score) occurred after aspiration with a green-hub needle without local anaesthetic: 5·1(0·4) cm (F = 10·28, 3112 d.f., P < 0·01, ANOVA). The level of discomfort and mean pain scores expressed by patients in the three remaining groups were similar and not statistically different (P = 0·94–1·0, Bonferroni correction).

The pain reported by the patients was influenced by which surgeon performed the aspiration (*Table 2*). Overall, combining the four study groups, there was a difference of 1·2 cm between mean(s.e.m.) pain scores for the two surgeons involved in the study: M.W.K. 4·0(0·3) cm *versus* I.R.D. 2·8(0·3) cm (F = 7·33; 1114 d.f., P < 0·01, ANOVA). When the mean pain scores were assessed on a needle by needle basis (*Table 2*), a difference still existed between the two operators but it was not statistically significant (P = 0·16–0·91). The lower mean pain score was not associated with a corresponding increase in the rate of acellular (C1) samples: I.R.D. 5 per cent (three of 60) *versus* M.W.K. 9 per cent (five of 56) (P > 0·05).

The surgeon's impression of the tumour (benign or malignant) appeared to affect the patient's reaction to FNAC. However, whilst patients thought by the surgeon clinically to have cancer did report a higher mean pain score (4·1(0·5) *versus* 3·2(0·3) cm), the difference was not statistically significant (t = 1·63; 114 d.f., P = 0·11).

Table 1 Comparison of pain scores for breast fine-needle aspiration cytology analysed by needle size and use of local anaesthetic

Needle size	No. of samples	Mean (s.e.m.) pain score (cm)
Without local anaesthetic		
Green	35	5·1(0·4)
Blue	31	2·9(0·4)
With local anaesthetic		
Green	23	2·1(0·4)
Blue	27	3·0(0·4)

F = 10·28, 3112 d.f., P < 0·01 (ANOVA)

Discussion

FNAC of the breast is a valuable technique[1–3] that may be painful or distressing. Studies have shown that needle size and the use of local anaesthetic have no effect on the diagnostic accuracy of breast FNAC[5,6]. There are claims that FNAC of the breast is not painful and that local anaesthetic is unnecessary[7,8].

This study shows that patients experience less pain during breast FNAC if a blue-hub (23 G) needle is used. Whilst local anaesthetic was found to decrease the pain of breast FNAC when using a green-hub needle, there was not a similar improvement when combined with a blue-hub needle. The combination of a blue-hub needle and local anaesthetic was more painful than using the needle alone.

The technique of breast FNAC is operator dependent[12] and similar results with regard to the pain of breast FNAC were demonstrated in this study. Despite this, a green-hub

Table 2 Comparison of the effect of different-sized needles and use of local anaesthetic on pain scores of breast fine-needle aspiration cytology, for each surgeon

Needle size	No. of samples	Mean (s.e.m.) pain score (cm) M.W.K.	I.R.D.	P*
Without local anaesthetic				
Green	35	5·1(0·5)	5·0(0·7)	0·91
Blue	31	3·2(0·8)	2·7(0·5)	0·60
With local anaesthetic				
Green	23	3·0(0·9)	1·7(0·5)	0·17
Blue	27	3·5(0·6)	2·3(0·5)	0·16
All groups	116	4·0(0·3)	2·8(0·3)	<0·01

*Two-sample t test

needle without local anaesthetic remained the most painful combination for breast FNAC regardless of which surgeon performed the aspiration.

The reason for the difference in pain scores between surgeons is unclear as both used an identical technique. It is possible that I.R.D. exerted less force with each pass of the needle, although this was not reflected by an increase in acellular (C1) samples. Another possible explanation is that, because I.R.D. was responsible for recording the pain score from every patient, women upon whom I.R.D. performed the aspiration may have been more self-conscious of expressing a high pain score than those whose FNAC samples were taken by M.W.K.

A blue-hub needle without local anaesthetic is the most appropriate for breast FNAC in the interests of diagnostic accuracy, patient comfort and ease of application. Alternatively, clinicians preferring the tactile sensation provided by a green-hub needle should consider using local anaesthetic for the benefit of patients. Future studies may need to address whether a larger volume of local anaesthetic left for longer than 3 min might have a greater effect on pain scores.

Acknowledgements

This study was performed within a research fellowship funded by the Royal College of Surgeons of England and the Juniper Trust.

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Randomized clinical trial

Long-term results of a randomized clinical trial between laparoscopic hernioplasty and Shouldice repair

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Background: At present only short-term follow-up data are available to compare endoscopic and conventional hernia surgery. This paper presents data from a randomized study 6 years after initial recruitment.

Methods: In 1993 a randomized comparative study of transabdominal preperitoneal (TAPP) and Shouldice repair was commenced. Endpoints were rate of recurrence, late complications, complaints and patient satisfaction.

Results: The rate of recurrence in the TAPP group was one (2 per cent) of 48 patients and in the Shouldice group two (5 per cent) of 43. Only five patients in the Shouldice and three in the TAPP group reported slight discomfort in the inguinal region at 6-year follow-up. In neither group was chronic pain syndrome observed. Altogether, 46 (96 per cent) of 48 patients in the TAPP group and 35 (81 per cent) of 43 of those having the Shouldice procedure stated complete satisfaction with the hernia repair.

Conclusion: Long-term evaluation demonstrated greater satisfaction with the result of the repair in the endoscopic group. The difference between the groups in the recurrence rate was not significant, because of the small numbers. The TAPP method appears to be an effective surgical alternative in patients with inguinal hernia.

Paper accepted 16 December 1999

British Journal of Surgery 2000, 87, 780–783

Introduction

The introduction of minimally invasive techniques to general surgery have brought into question the need for conventional surgical techniques for inguinal hernia repair. Several randomized comparative studies of endoscopic and conventional procedures have been undertaken in the past few years in an attempt to determine the optimal surgical technique[1]. In trials conducted in English-speaking countries, tension-free procedures were chosen more frequently as control methods, whereas in German-speaking countries the Shouldice repair was used as a standard for comparison. What these studies share is a lack of long-term follow-up data.

This study reports the 6-year follow-up results of a prospective randomized study comparing the transabdominal preperitoneal (TAPP) endoscopic technique with the Shouldice repair.

Objectives and study design

In 1995, a phase IIb randomized comparative study of TAPP with Shouldice repair was reported[2]. The study included unilateral, reducible, primary hernias of men and women with a minimum age of 18 years and a low anaesthetic risk (American Society of Anesthesiologists grade I–II). Patients with scrotal hernias, as well as those with previous lower abdominal surgery which was considered to present a potential obstacle to a transperitoneal endoscopic procedure, were excluded from the study. Laparoscopic repairs were performed by surgeons experienced in endoscopic procedures with at least 25 previous TAPP repairs. The Shouldice repair was performed according to the technique of Schumpelick[3], which had been the standard procedure for inguinal hernia repair in this unit at the beginning of the study. All surgeons and residents who performed those repairs were experienced in this technique or supervised by an expert to guarantee a standardized procedure.

All patients were operated on under standard ethrane anaesthesia. The Shouldice operation was performed employing the technique outlined by Schumpelick *et al.*[3]. The TAPP procedure was performed with a 10 × 12-cm polypropylene mesh (Ethicon, Norderstedt, Germany) placed in a preperitoneal position. Following the incision of the mesh, the deep inguinal ring was reconstructed overlapping the two sides of the slit. The overlapping adaptation of the mesh as well as the fixation were accomplished by means of eight to ten titanium clips (EMS Herniostate; Ethicon).

Endpoints of the study were postoperative pain, mobilization, convalescence (length of disability) and complications. Patient mobilization during the hospital stay was self-determined; its duration was measured and recorded daily. The time period from hospital admission to the resumption of normal work defined the length of disability.

In the long-term follow-up the rate of recurrence, late complications and complaints, as well as patient satisfaction, were recorded. The two latter assessments were evaluated with the help of a visual analogue scale (VAS)[4] (10 cm, 0–100), in which zero represented extreme dissatisfaction and 100 complete satisfaction. For complaints, zero was registered for no complaints, whereas 100 represented the highest degree of complaints. Using the same assessment scales, a re-evaluation of the randomized patients was undertaken in 1999.

Analysis of the data was performed with the help of an established computer databank (Excel; Microsoft). Differences between the two surgical groups were measured with the Wilcoxon rank sum test and the χ^2 test. $P < 0·05$ was considered significant.

Results

A total of 102 patients was randomized to either the Shouldice ($n = 48$) or the TAPP ($n = 54$) group (*Table 1*). The median operating time in the conventional therapy group was 47·5 (range 30–110) min, whereas 65 (30–135) min was needed in the endoscopic group. The morbidity rate was four (7 per cent) of 54 for TAPP *versus* four (8 per cent) of 48 in the conventional group. Reoperation after Shouldice repair became necessary in two patients because of a postoperative testicular swelling and in another case because of an inguinal haematoma. Laparoscopic haematoma evacuation after endoscopic surgery was required in two patients, also because of an inguinal haematoma. No wound or mesh infection was noted, nor were there any fatal complications. The length of self-determined postoperative mobilization as well as the consumption of analgesics demonstrated significant advantages for endoscopically treated patients (*Tables 2* and *3*). The postoperative period of disability was a median of 21 days following endoscopic surgery and 38 days after conventional surgery ($P < 0·001$).

After 6 years, four patients in the TAPP group and three in the Shouldice group were lost to follow-up and a further two patients in each group had died. Therefore, 48 patients (89 per cent) from the original TAPP group and 43 (90 per cent) from the original Shouldice group were available for re-evaluation. In the conventional group, two patients had had a recurrence (recurrence rate 5 per cent). The first patient had a medial hernia 60 months after operation and the second a lateral hernia 34 months after surgery. To date, reoperation for recurrence has been performed on only one patient, using the TAPP method. In the TAPP group, one patient had had a recurrence (recurrence rate 2 per cent), which was diagnosed 24 months after operation. During the TAPP reoperation, a medial hernia was also found as a consequence of using too small a mesh for the primary direct hernia.

As an incidental finding during follow-up, a contralateral inguinal hernia was diagnosed in five of 48 patients in the TAPP group and in four of 43 in the Shouldice group. Only five patients who had the Shouldice operation and three

Table 1 Characteristics of patients in the two treatment groups

	TAPP ($n=54$)	Shouldice ($n=48$)
Sex ratio (M : F)	48 : 6	43 : 5
Age (years)*	53 (18–79)	56 (22–85)
BMI*	24·3 (18·3–30·0)	24·8 (17·3–32·6)
Type of hernia		
Direct	15	19
Indirect	34	26
Combined	5	3

*Values are median (range). BMI, body mass index; TAPP, transabdominal preperitoneal

Table 2 Length of self-determined postoperative mobilization during hospital stay

	Length of mobilization (min)		
Time after operation	TAPP	Shouldice	P*
Day 1	60 (5–285)	15 (0–300)	0·0002
Day 2	110 (5–720)	45 (10–700)	0·0004

Values are median (range). TAPP, transabdominal preperitoneal. *Wilcoxon rank sum test

Table 3 Number of patients not receiving postoperative analgesics

Time after operation	TAPP ($n=54$)	Shouldice ($n=48$)	P*
Day 1	43 (80)	11 (23)	< 0·001
Day 2	50 (93)	21 (44)	< 0·001
Day before release	54 (100)	37 (77)	0·01 > 0·001

Values in parentheses are percentages. TAPP, transabdominal preperitoneal. *χ^2 test having the TAPP procedure still had any complaints at the 6-year follow-up (*Table 4*). The range on the VAS for complaints was 10–18 (mean 14·6) for the Shouldice group and 4–26 (mean 18·9) for the TAPP group (*P* not significant). With regard to patient satisfaction, 46 of 48 patients in the TAPP group and 35 of 43 who had the Shouldice procedure indicated complete satisfaction with the postoperative results (*P* not significant), but two of the patients having the laparoscopic approach and eight of those in the Shouldice group were less than 100 per cent satisfied ($P < 0·05$). Neither of the two therapeutic options led to a chronic pain syndrome. Median follow-up of patients is 70 months.

Table 4 Number of patients with complaints during postoperative follow-up

Time after operation	TAPP	Shouldice	*P**
1 month	12 of 54 (22)	28 of 47 (60)	< 0·05
1 year	8 of 53 (15)	22 of 48 (46)	< 0·05
6 years	3 of 48 (6)	5 of 43 (12)	n.s.

Values in parentheses are percentages. TAPP, transabdominal preperitoneal; n.s., not significant. *χ^2 test

Discussion

Since Ger[5] described the first endoscopic technique in 1982, a series of technical modifications has been made in laparoscopic and open hernia repairs, pressed by the need to avoid recurrences. Since 1993, several studies have evaluated the different therapeutic options in inguinal hernia treatment. Included in the 26 comparative studies reported in the literature[2,6–30] are such techniques as the transperitoneal TAPP, the absolutely extraperitoneal TEP (totally extra peritoneal preperitoneal) and, in only one study, the intraperitoneal onlay mesh (IPOM) technique. According to traditional differences, the choice of control therapies varied from conventional suture techniques to tension-free repairs. Early results from these studies showed an advantage for endoscopic repair with regard to postoperative pain (20 of 26 studies demonstrated significantly less pain) and duration of disability (18 of 23 studies showed a shorter duration, of which 12 had a statistically significant result). Despite different control techniques (i.e. conventional tension-free or suturing procedures), the results of these studies were largely similar.

In these trials, there was no difference in the evaluation of the rate of complications. However, the majority of comparative studies showed a significantly longer operating time for the endoscopic techniques. Because of short follow-up periods and small patient numbers, evaluation of hernia recurrence was carried out in only two studies. In these trials a significant advantage was shown in favour of endoscopy (TAPP 0 per cent *versus* Shouldice 3 per cent; TEP 3 per cent *versus* 6 per cent for various conventional techniques)[13,16]. However, differences, particularly in endoscopic techniques and the level of surgical experience, probably affected the final results of these studies in adding to considerable spread of data.

Despite the promising results of these studies, the lack of long-term follow-up data is a considerable shortcoming. Only one study (IPOM *versus* Bassini) gave long-term follow-up data[29]. In this trial late complications were seen in 22 per cent of patients having the endoscopic procedure (IPOM). The authors concluded that the endoscopic IPOM technique is unsuitable for inguinal hernia repair because of a high recurrence rate (43 per cent).

The present results (median follow-up 70 months), however, suggest that the TAPP technique represents a safe method for effective inguinal hernia repair with minimal risk of long-term complications. Fewer recurrences occurred in the endoscopic group than in the control group, although the difference was not statistically significant because of the limited numbers. Results from previously published prospective series of TAPP hernioplasty showed recurrence rates of less than 1 per cent, thus strongly supporting the advantage of endoscopy with regard to hernia recurrence[30,31].

There was significantly less pain in the TAPP group up to 1 year after operation, but the difference was not statistically significant in the long-term follow-up. Thus, despite the implantation of a large preperitoneal polypropylene mesh, this foreign body is well tolerated and does not lead to chronic pain syndrome. Patient satisfaction also showed a tendency in favour of TAPP, even though this can be interpreted only as an indicator of the positive acceptance of the endoscopic method.

After 10 years of endoscopic hernia surgery, further randomized studies are desirable to confirm the long-term benefit of the laparoscopic approach employed in this study.

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Original article

Beneficial effects of arterialization of the portal vein on extended hepatectomy

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Background: Extended hepatectomy may result in postoperative liver failure. The aim of this study was to evaluate the effects of arterialization of the portal vein on oxygen supply, hepatic energy metabolism and liver regeneration after extended hepatectomy.
Methods: Portal haemodynamics were evaluated 0 or 10 days after arterialization of the portal vein in three experimental groups: 85 per cent partial hepatectomy, 85 per cent partial hepatectomy 10 days after arterialization of the portal vein and 85 per cent partial hepatectomy 10 days after ligation of the hepatic artery. Survival rates, weight of the regenerating liver, levels of adenine nucleotides and hepatic energy charge were assessed.
Results: Arterialization of the portal vein caused a significant increase in partial pressure of oxygen and oxygen saturation. Portal blood flow 10 days after arterialization was significantly increased. Survival rate and weight of the regenerating liver in the group with arterialization of the portal vein were significantly higher than those in the other two groups. The group with arterialization of the portal vein showed the highest levels of adenosine 5′-triphosphate.
Conclusion: The increase in portal blood flow and oxygen supply produced by arterialization of the portal vein has beneficial effects on hepatic energy metabolism and liver regeneration, and leads to improved survival after experimental extended hepatectomy.

Paper accepted 1 November 1999

British Journal of Surgery 2000, 87, 784–789

Introduction

Hepatectomy is the standard surgical treatment for hepatic or biliary malignancy. Extended hepatectomy, with pancreaticoduodenectomy and/or vascular reconstruction, has recently been used in aggressive surgical treatment of cholangiocarcinoma and gallbladder carcinoma[1–5]. Standard hepatectomy is associated with relatively low morbidity, but extended hepatectomy may result in failure of the remaining liver tissue with fatal outcome[1–5]. The incidence of liver failure after hepatectomy is considered to depend on the capacity for regeneration of the remnant liver mass, which in turn is dependent on the supply of energy[6–9].

Hepatocyte energy is supplied mainly by the mitochondrial respiratory chain, which consumes about 90 per cent of the oxygen utilized by the liver[10,11]. A steady supply of oxygen is therefore necessary for liver regeneration after hepatectomy[12]. The liver has a dual blood supply, via the hepatic artery and portal vein. Approximately 80 per cent of the blood inflow to the liver is poorly oxygenated venous blood supplied by the portal vein. One of the methods of supplying sufficient blood with high oxygen saturation is arterialization of the portal vein. This technique was previously established as a clinical treatment for reducing the risk of liver failure after portacaval shunt[13–16]. In this study, experimental models were developed to study arterialization of the portal vein as a procedure for preventing liver failure. The aim was to evaluate the effects of arterialization of the portal vein on oxygen supply, hepatic energy metabolism and liver regeneration.

Materials and methods

Animals

Male Wistar rats, each weighing 250–300 g, were used for the experiments. All animals were kept in a temperature-controlled environment with a 12-h light–dark cycle, and allowed tap water and rat chow *ad libitum*. Animal research protocols were approved by the Chiba Animal Care

Committee, and the National Research Council's guide on the care and use of laboratory animals was followed.

Assessment of portal haemodynamics after arterialization of the portal vein

A laparotomy was made through a midline incision. The hepatic artery was gently isolated and divided at the hilus. A polyethylene tube (Intermedic PE-10; Clay Adams, Parsippany, New Jersey, USA) was cannulated into the proximal hepatic artery. The other end of the polyethylene tube was inserted into a vein which directly inflows to the portal vein. The tube was placed just on the hepatic side of the junction of the portal vein (*Fig. 1*). To measure changes in portal blood flow, the portal vein was gently isolated and an ultrasonic flow meter probe (Transonic Systems, Ithaca, New York, USA) was placed around the portal vein. Subsequently, portal vein pressure was measured by direct puncture with a 25-G needle, which was connected to a transducer (Model 128; F. Hoffman La Roche, Basel, Switzerland). At the same time, a blood sample was collected from the portal vein for gas analysis (OSM3 blood gas analyser; Radiometer, Copenhagen, Denmark). Measurements of portal blood flow and pressure, and gas analysis were carried out in rats without arterialization as a control group, and following arterialization (0 days) or 10 days after operation in experimental groups.

Survival study after 85 per cent partial hepatectomy

Rats were divided randomly into three groups: 85 per cent partial hepatectomy (group 1; $n = 18$), 85 per cent partial hepatectomy 10 days after arterialization of the portal vein (group 2; $n = 18$) and 85 per cent partial hepatectomy 10 days after ligation of the hepatic artery (group 3; $n = 18$).

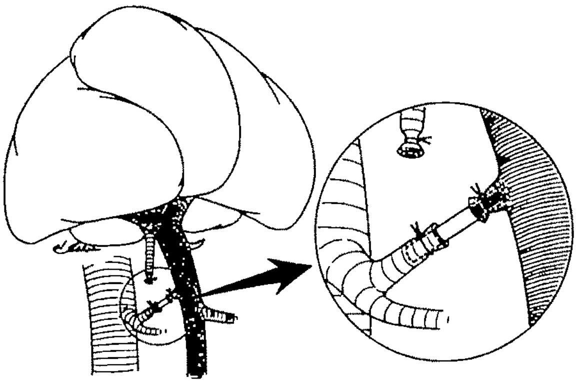


Fig. 1 Arterialization of the portal vein. Turbulent diffusion of arterial blood was visible through the wall of the portal vein

Eighty-five per cent partial hepatectomy was accomplished by standard 70 per cent partial hepatectomy plus removal of the right superior lobe. Twelve rats in each group were used for survival studies and the remaining six were used for assay of adenine nucleotides. All surviving rats in the survival study were killed 7 days after 85 per cent partial hepatectomy and wet liver weight was measured to evaluate the degree of liver regeneration.

Assay of adenine nucleotides

Liver tissue was obtained from six rats in each group 24 h after 85 per cent partial hepatectomy for assay of adenosine 5′-triphosphate (ATP), adenosine 5′-diphosphate (ADP) and adenosine 5′-monophosphate (AMP). The liver tissue was obtained from the caudal lobe of the remnant liver *in situ* using a freeze clamp precooled in liquid nitrogen and immediately stored at −80°C until analysis. The ATP, ADP and AMP concentration of the samples was determined as described by Lamprecht *et al.*[17] and Jaworek *et al.*[18]. The energy charge was then calculated as $(\text{ATP} + 0{\cdot}5\text{ADP})/(\text{ATP} + \text{ADP} + \text{AMP})$.

Statistical analysis

Results were expressed as mean(s.d.). Statistical analysis was performed using one-way analysis of variance and the Scheffe post hoc test. The Wilcoxon test was used for survival data. Statistical significance was set at $P < 0{\cdot}05$.

Results

Portal haemodynamics after arterialization of the portal vein

The influence of arterialization of the portal vein on portal blood gas analysis is summarized in *Table 1*. Arterialization of the portal vein caused a significant increase in partial pressure of oxygen and oxygen saturation, and a significant decrease in partial pressure of carbon dioxide (all $P < 0{\cdot}01$). However, no significant differences in portal blood gas analysis were observed between 0 and 10 days after arterialization. Portal haemodynamic changes are shown in *Fig. 2*. Portal vein pressure 10 days after arterialization was significantly higher than that in the control group ($P < 0{\cdot}01$), but there were no significant differences between 0 and 10 days after arterialization. On the other hand, portal flow 10 days after arterialization was significantly increased compared with both that in the control group ($P < 0{\cdot}01$) and that 0 days after arterialization ($P < 0{\cdot}01$). It was confirmed that good patency of the anastomosis had been maintained for 10 days after operation in all cases, and also 20 days after

Table 1 Blood gas analysis of the portal vein

	Control	After arterialization of the portal vein	
		0 days	10 days
pH	7·34(0·01)	7·39(0·03)	7·42(0·04)
P_{CO_2} (mmHg)	49·1(3·1)	39·6(1·8)*	37·5(1·3)*
P_{O_2} (mmHg)	45·1(3·3)	70·8(3·5)*	71·3(7·2)*
Base excess (mmol/l)	1·9(1·7)	0·6(1·7)	0·3(2·3)
Oxygen saturation (%)	78·9(4·1)	92·9(1·5)*	94·1(1·6)*

Values are mean(s.d.) ($n = 4$ per group). P_{CO_2}, partial pressure of carbon dioxide; P_{O_2}, partial pressure of oxygen; $^*P < 0{\cdot}01$ *versus* control (one-way analysis of variance and Scheffe post hoc test)

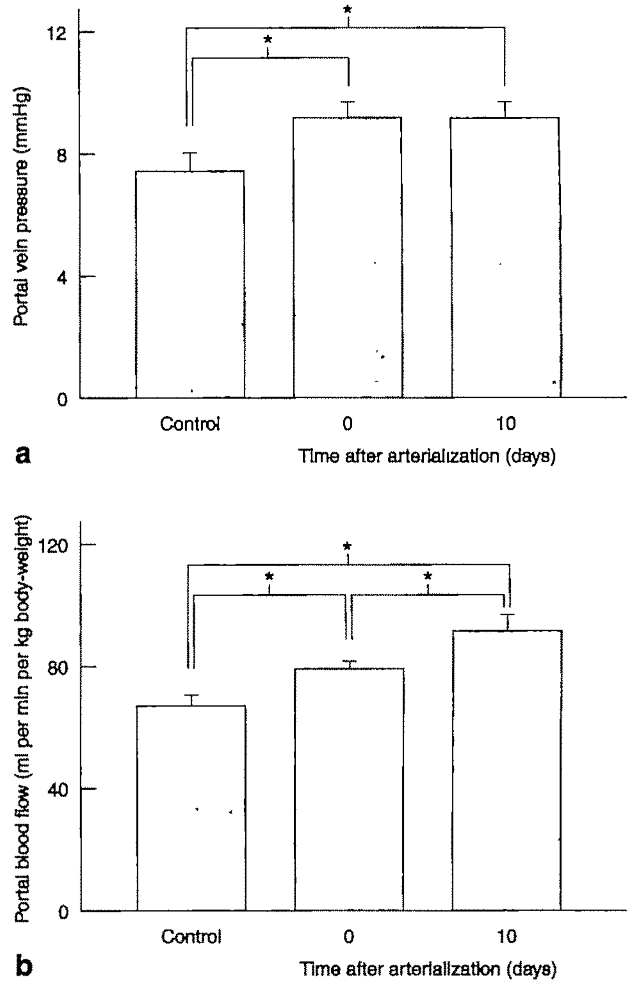


Fig. 2 Mean(s.d.) changes in
a portal vein pressure and
b portal flow after arterialization of the portal vein ($n = 4$ in each group). $^*P < 0{\cdot}01$ (one-way analysis of variance and Scheffe post hoc test)

operation in a preliminary study by investigating turbulent diffusion of arterial blood through the portal vein. There were no significant changes in liver weight after arterialization of the portal vein (normal liver weight 3·64(0·09) *versus* 3·71(0·17) mg per 100 g body-weight 10 days after arterialization). Histological examination of the liver tissue revealed no serious changes, except slight inflammation in periportal regions after arterialization (data not shown).

Survival study

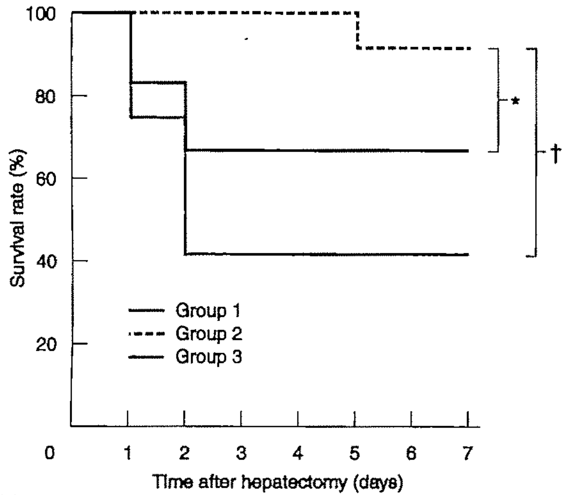
Survival in the group subjected to arterialization of the portal vein was significantly better than that in the other two groups (*Fig. 3*). The survival rates 7 days after hepatectomy were 67, 92 and 42 per cent for groups 1, 2 and 3 respectively. Furthermore, the regenerating liver weight 7 days after 85 per cent partial hepatectomy in the group with arterialization of the portal vein (group 2, 2·56(0·14) mg per 100 g body-weight) was significantly higher than that in the other two groups (group 1, 2·38(0·09) mg per 100 g ($P < 0{\cdot}05$); group 3, 2·34(0·08) mg per 100 g ($P < 0{\cdot}01$)).

Levels of ATP in the regenerating liver 24 h after 85 per cent partial hepatectomy are shown in *Fig. 4*. The levels of ATP in rats with arterialization of the portal vein were significantly higher than those in animals with ligation of the hepatic artery ($P < 0{\cdot}01$) or hepatectomy alone ($P < 0{\cdot}05$). However, there were no significant differences in the levels of energy charge 24 h after 85 per cent partial hepatectomy among the three groups (group 1, 0·43(0·08); group 2, 0·53(0·04); group 3, 0·41(0·09)).

Discussion

The liver consumes about 20 per cent of the total oxygen used by the human organism[11]. In the liver, oxygen is used primarily for the oxidation of substrates, most of which results in the preservation of free energy as ATP. This ATP serves as the principal and immediate donor of free energy in biological systems[10,11]. Under normal conditions, most cells have an adequate oxygen concentration and mitochondria are always saturated with oxygen. However, under critical conditions, hepatocytes may have an oxygen concentration at which mitochondrial respiration and ATP synthesis are partially oxygen limited[19]. In such cases, oxygen is considered to be essential for the improvement of energy metabolism. Portal blood, which accounts for almost 80 per cent of the hepatic blood supply, is rich in nutrients absorbed by the intestine, but its oxygen content is low.

Arterialization of the portal vein was originally established as a clinical treatment for reducing the incidence of



No. at risk								
Group 1	12	10	7	7	7	7	7	7
Group 2	12	12	12	12	12	11	11	11
Group 3	12	9	5	5	5	5	5	5

Fig. 3 Survival curves after 85 per cent partial hepatectomy (group 1; $n = 12$), 85 per cent partial hepatectomy 10 days after arterialization of the portal vein (group 2; $n = 12$) and 85 per cent partial hepatectomy 10 days after ligation of the hepatic artery (group 3; $n = 12$). $^*P < 0{\cdot}05$, $\dagger P < 0{\cdot}01$ (Wilcoxon test)

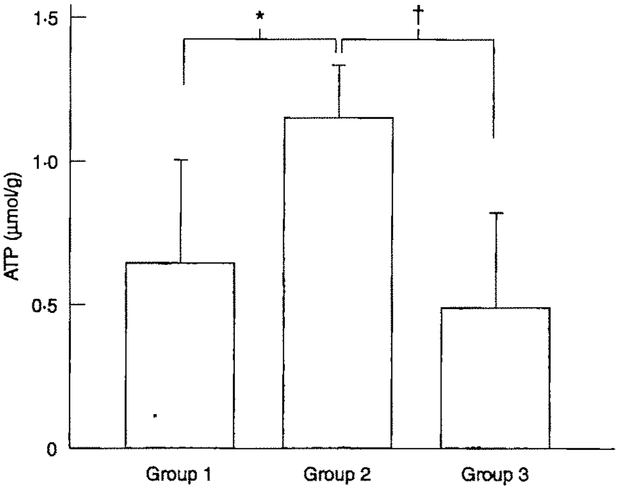


Fig. 4 Mean(s.d.) levels of adenosine 5′-triphosphate (ATP) in the regenerating liver 24 h after 85 per cent partial hepatectomy (group 1; $n = 6$), 85 per cent partial hepatectomy 10 days after arterialization of the portal vein (group 2; $n = 6$) and 85 per cent partial hepatectomy 10 days after ligation of the hepatic artery (group 3; $n = 6$). $^*P < 0{\cdot}05$, $\dagger P < 0{\cdot}01$ (one-way analysis of variance and Scheffe post hoc test)

encephalopathy and preventing liver failure in high-risk patients after portacaval shunt operations[13–16]. In animal liver transplantation models, some investigators have evaluated liver viability and energy metabolism after temporary arterialization of the portal vein[20–22]. There are also clinical reports of four cases which showed the method and indication for arterialization of the portal vein as treatment for thrombosis of the portal vein in liver transplantation[23,24]. It was reported previously that partial portal arterialization using a splenic artery–vein shunt improved liver function and inhibited the increase of plasma endotoxin levels in dog hepatectomy models[25]. However, there have been few reports that focus on liver regeneration and energy metabolism after arterialization of the portal vein.

Based on the findings that portal flow 10 days after arterialization was significantly higher than that immediately after arterialization, and that rats could not survive simultaneous hepatectomy with arterialization because of the extreme surgical stress induced by portal vein clamping and the longer operation time (data not shown), a survival study of 85 per cent partial hepatectomy 10 days after arterialization of the portal vein was designed. This study revealed the beneficial effects of arterialization of the portal vein on survival rates after 85 per cent partial hepatectomy. On the other hand, no effect of arterialization on hepatic energy metabolism was demonstrated. It has been reported that the regenerating liver requires an enormous amount of energy for its increased metabolic load. Mitochondria play a major role in energy metabolism in the early phase of liver regeneration through increased mitochondrial oxidative phosphorylation[7–9]. It was therefore predicted that increased oxygen supply provided through arterialization of the portal vein would cause an increase in ATP and energy charge in the regenerating liver after hepatectomy. As expected, the levels of ATP in the group with arterialization of the portal vein were significantly higher than those in the other two groups. However, no significant differences in the levels of energy charge were found. This may be related to the fact that the liver specimens were collected 24 h after hepatectomy *in situ* and surviving rats may have shown higher levels of energy charge than those which died within 24 h. However, Yoshioka *et al.*[26] have shown that the regenerating liver requires increased amounts of oxygen, and that hepatic venous oxygen saturation may reflect oxygen metabolic status and the regenerative process in the remnant liver after hepatectomy. Nonami *et al.*[12] have also documented that the hyperdynamic circulation induced by dopamine or dobutamine increases oxygen consumption and extraction of lactate in the remnant liver after hepatectomy. Moreover, the present study showed that the weight of the regenerating liver 7 days after 85 per cent partial hepatectomy was significantly greater in the group with arterialization than in the other two groups. These findings provide evidence that an increase in portal blood flow and oxygen supply was beneficial to liver regeneration after hepatectomy.

Partial arterialization of the portal vein may be applicable clinically to patients with advanced hepatobiliary malignancy, because successful splenic and mesenteric arteriovenous shunts have been reported to be better tolerated in patients than in experimental models[25,27,28]. The long-term consequence of arterialization of the portal vein is prehepatic portal hypertension, which might be corrected by interventional or surgical interruption of the arterioportal fistula[24,27].

In conclusion, it has been demonstrated that portal blood flow and oxygen supply are increased after arterialization of the portal vein. These increases have beneficial effects on hepatic energy metabolism and liver regeneration, and lead to improved survival after hepatectomy. This study suggests that arterialization of the portal vein may be a clinically useful technique for preventing liver failure after hepatectomy.

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Original article

Experimental study of a novel fibrin sealant for achieving haemostasis following partial hepatectomy

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Background: Ensuring adequate haemostasis is a major difficulty in the field of liver surgery. This study aimed to evaluate a novel fibrin sealant (Vivostat), designed for autologous preparation, in a porcine model of partial hepatectomy.

Methods: Thirty-six Large White Landrace pigs underwent partial left hepatectomy by finger fracture under portal vascular inflow occlusion. Animals were randomized to treatment of the resected surface with either fibrin sealant (Vivostat, $n = 12$) or regenerated oxidized cellulose gauze (Surgicel, $n = 12$), or were left untreated (controls, $n = 12$). Blood loss from the resection margin was measured at 2-min intervals for 10 min, and the time to haemostasis was recorded. Following complete haemostasis the animals recovered for 7 days.

Results: Median (range) blood loss in the control group was 94·3 (17·3–467·0) g, and was significantly reduced with Vivostat (13·8 (5·5–150·9) g) and Surgicel (22·8 (5·8–67·3) g). Median (range) time to haemostasis in controls (31 (12–52) min) was also significantly reduced by Vivostat (8 (0–32) min) and Surgicel (10 (0–19) min) (both $P < 0.001$ *versus* controls, Kruskal–Wallis test).

Conclusion: The novel fibrin sealant, Vivostat, is as effective as Surgicel cellulose gauze in achieving haemostasis after porcine partial hepatic lobectomy.

Paper accepted 14 December 1999

British Journal of Surgery 2000, 87, 790–795

Introduction

Morbidity, mortality and long-term outcome after liver surgery are adversely affected by blood loss during the procedure[1–4]. Of the many methods available for reducing intraoperative blood loss, those most commonly used are ultrasonic dissection[5], topically applied haemostatic agents[6], argon beam coagulation[7] and lowering central venous pressure[8].

Regenerated oxidized cellulose gauze (Surgicel; Johnson and Johnson, High Wycombe, UK) is one of the most commonly used topical agents, although concerns exist relating to potential adverse tissue reactions to oxidized cellulose[9–11]. Fibrin sealants have also been investigated extensively over the past 15 years, but despite effective control of small vessel ooze[12–14] there is concern over their safety because they are derived from pooled human blood or involve the use of exogenous thrombin and other animal-derived proteins[15]. The former is associated with the risk of human immunodeficiency virus or hepatitis virus transmission, and the latter causes concern because of possible transmission of bovine spongiform encephalopathy[16–19] as well as the potential for immunological reactions to foreign proteins[20,21].

A novel fibrin sealant system (Vivostat; ConvaTec, Uxbridge, UK. Vivostat is not currently available for sale; it is an investigational device in the USA) has been developed which avoids these potential hazards by deriving the fibrin sealant from the patient's own blood[22]. Preliminary data suggest that it is an effective haemostatic agent[23]. The present study was undertaken to assess the efficacy of Vivostat system-derived fibrin sealant in liver surgery using a reproducible and clinically relevant large animal model.

Materials and methods

The Vivostat system

The Vivostat system is a medical device for the preparation of autologous fibrin sealant from 120 ml of a patient's own blood in the operating room. The system is fully automated and microprocessor controlled, comprising three distinct components:

1 A processor unit that drives and controls the production of a concentrated fibrin I solution from whole blood within a disposable preparation unit.
2 An applicator unit that houses the fibrin I and buffer cartridges and feeds the solutions into the application pen through a multilumen catheter.
3 A disposable single-use patient kit which contains everything needed to prepare and apply the fibrin sealant, including a preparation unit into which blood is collected and in which the biochemical process to produce the fibrin I solution occurs, and a Spraypen applicator which allows the fibrin I solution to be applied accurately and evenly to the target tissue.

After drawing 120 ml of blood into the preparation unit, it is mixed with trisodium citrate as anticoagulant. Centrifugation separates the cells and results in about 60 ml of platelet-poor plasma. The biochemical process is initiated by batroxobin, which acts upon the fibrinogen in the patient's plasma to produce the fibrin I solution. Completion of the process depends entirely on endogenous thrombin to form a chemically stable, cross-linked fibrin II polymer on contact with the target tissue. More detailed descriptions of the system and biochemical process have been reported[22,23].

For the purposes of this porcine study, the fibrin sealant was prepared from pooled human plasma. The fibrin sealant was stored at −20°C, and thawed at 37°C when required.

Study design

Thirty-six Large White Landrace crossbred pigs (20 ± 5 kg) (PSS Pig Supplies and Services) were allocated randomly into three groups to receive either Vivostat fibrin sealant ($n = 12$), Surgicel ($n = 12$) or no treatment (controls, $n = 12$). The animals were premedicated with azaperone, 5 mg/kg intramuscularly (Janssen Animal Health, Grove, Oxford, UK) and antibiotic prophylaxis of amoxycillin 15 mg/kg intramuscularly (Janssen Animal Health). Anaesthesia was induced with ketamine (100 mg/ml clinical dose, 5 mg/kg intravenously) and maintained with halothane, nitrous oxide and oxygen delivered by endotracheal intubation. Anaesthesia was monitored during the procedure by recording the pulse rate, oxygen saturation and core body temperature. Intravenous access was secured in the external jugular vein to allow fluid replacement during the operation.

The operation was carried out using aseptic technique. The skin was prepared with aqueous povidone–iodine (Betadine; Seton Healthcare, Oldham, UK) and sterile draped. A transverse laparotomy incision with midline extension allowed exposure of the liver, which was mobilized to reveal the four anatomical lobes (right and left, medial and lateral). As with human liver resection, the hepatoduodenal ligament was dissected to allow portal triad occlusion. A standard position at the inferior margin of the vascular pedicle of the left lateral lobe was identified for resection. The circumference of resection was recorded and, under portal vascular inflow occlusion, excised using diathermy for the liver capsule followed by blunt dissection using finger fracture. Vessels or bile ducts greater than 2 mm in diameter revealed at the resection surface were counted, ligated (2/0 polyglactin) and divided. The resected liver was weighed. The resected margin and surrounding area were swabbed free of blood and the swabs were collected in containers and labelled for analysis of blood loss (gravimetric methods).

The resected surface was then either treated with Vivostat or Surgicel, or left untreated according to randomization. The fibrin sealant was applied topically using the Spraypen applicator progressively across the cut surface with a single coating. Sufficient fibrin sealant was applied to provide an obvious white layer on the cut surface. After treatment, inflow occlusion was continued for 3 min and the total inflow occlusion time noted. Following removal of the clamps, blood loss was collected from the cut surface by swabs at 2-min intervals for 10 min. If complete haemostasis was not achieved by this time, additional treatment was allowed. Once haemostasis was established, the abdomen was closed using 1/0 polypropylene mass suture to the abdominal wall, polyglactin to the subcutaneous fat and 1/0 nylon mattress sutures to the skin.

The animals were monitored regularly and allowed food as normal and water *ad libitum* on recovery from anaesthesia. After 7 days the animals were premedicated and anaesthetized as described previously. The previous laparotomy incision was reopened. Any intra-abdominal collections were assessed and the resected liver surface was examined for adhesions (*Table 1* shows the adhesion grading system) and for the presence or absence of haemostatic agent. The animal was then killed by lethal injection of Euthatol, 30 ml (Rohne Merieux, Dublin, Ireland) and a tissue sample was taken from the resected surface extending into the parenchyma. This was fixed in neutral buffered formaldehyde and processed to wax embedding. Sections were cut at 5 μm, stained with haematoxylin and eosin, and histopathological analysis was performed.

All sections were examined by two independent histopathologists, blind to randomization, for a series of histopathological parameters. The reaction to injury, interphase liver and underlying normal tissue were

Table 1 Grading system for assessment of adhesions following partial hepatectomy and treatment of the resected surface with Vivostat, Surgicel or no treatment (control)

Grade	Description
0	No adhesions
1	One or two weak adhesions
2	More than two adhesions that produce some tissue damage on separation by blunt dissection
3	Adhesions throughout the abdominal cavity, some requiring sharp dissection
4	Very aggressive adhesions throughout the abdominal cavity causing considerable damage on dissection

Table 2 Comparison of measurable parameters as a result of partial hepatectomy in pigs

	Control	Vivostat	Surgicel
No. of vessels ligated	4 (3–6)	3 (2–5)	4 (2–5)
Circumference of resection margin (cm)	19·3 (17·5–22·5)	19·6 (16·3–21·5)	19·5 (16·0–21·5)
Area of resected surface (cm^2)	29·7 (24·4–40·3)	30·5 (21·1–36·8)	30·1 (20·4–36·8)
Wet weight of resected liver (g)	75·3 (52·9–90·5)	65·3 (40·6–104·7)	75·1 (47·9–91·5)
Portal occlusion time (min)	12 (10–15)	12·5 (11–17)	13 (10–16)

Values are median (range). The Kruskal–Wallis test for differences between groups was performed by pairwise treatment comparisons from analysis of variance on transformed data (log transformation) and showed no significant differences

assessed for the following histopathological parameters: demarcation of reactive tissue from interphase tissue, bile duct proliferation, acute and chronic inflammation, presence of fibrin sealant, granuloma, calcification, necrotic hepatocytes, giant cells, eosinophilia, lobular accentuation, portal fibrosis and inflammation, lymphoid follicles and lobules.

Blood samples were taken from all animals before the first operation and before killing (2 × 5 ml sodium citrate, 5 ml ethylenediamine tetra-acetic acid) for full blood counts, serum iron estimation, total iron binding capacity, ferritin concentration, clotting profile, serum electrolytes and liver function tests.

Statistical analysis

Treatment groups were compared for the number of vessels ligated, portal clamp time, circumference of resection, area of resected surface, weight of resected liver, blood loss and time to haemostasis, using the Kruskal–Wallis test for overall significance, taken at the 5 per cent confidence level. Where the overall difference was significant, further analysis of pairwise treatment group comparisons was performed with a one-way analysis of variance on raw or transformed data as appropriate. Intergroup differences in histopathological parameters were analysed with the Wilcoxon rank sum test.

Results

Portal inflow occlusion was not well tolerated in these pigs; the majority developed tachycardia (60–90 beats per min at baseline *versus* 240–260 beats per min during inflow occlusion) and reduced oxygen saturation levels that resolved slowly on restoring portal inflow. The surgical technique proved to be consistent by analysis of resection circumference, resection surface area, number of vessels ligated, wet weight of resected tissue and portal occlusion time for each procedure (Kruskal–Wallis test) (*Table 2*).

Haemostasis

Application of Vivostat and Surgicel was associated with a significant reduction in blood loss compared with controls ($P < 0{\cdot}001$, Kruskal–Wallis test), with no significant differences between the active treatment groups ($P = 0{\cdot}15$) (*Fig. 1*). The median blood loss in the 10 min following resection was 13·8 (range 5·5–150·9) g with Vivostat, compared with 22·8 (5·8–67·3) g and 94·3 (17·3–467·0) g in the Surgicel and control groups respectively (gravimetric analysis of blood loss). The volume of blood loss was typically 100–150 ml in the control group. The measurement of blood loss after the initial 10-min interval was biased by the additional methods of haemostasis permitted. Application of Vivostat and Surgicel significantly reduced

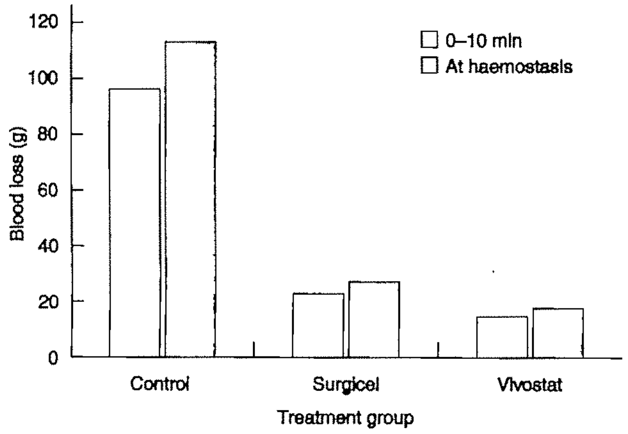

Fig. 1 Median blood loss following partial hepatectomy and treatment of the resected surface with Vivostat, Surgicel or no treatment (control) ($n = 12$ for all groups)

the time to haemostasis compared with controls ($P < 0{\cdot}001$, Kruskal–Wallis test); haemostasis was achieved in a median of 8 (range 0–32) min with Vivostat and 10 (0–19) min with Surgicel, compared with 31 (12–52) min in untreated controls. The mean(s.d.) volume of Vivostat applied was 2·3(0·6) ml.

Postoperative recovery

Nine pigs died during the study from causes unrelated to partial hepatectomy. One died from malignant hyperthermia and another from spontaneous pneumothorax before the operation was performed. Three animals died following portal inflow occlusion. These animals had marked hyperkalaemia and acidosis after clamp removal and the probable cause of death was reperfusion injury. Four animals died from small bowel volvulus, confirmed by autopsy; this is a recognized complication of laparotomy in pigs. The volvulus was not related to adhesion formation. Thirty-six animals survived to day 7 and data from only these animals are included.

At second laparotomy on day 7, all 36 animals had extensive adhesions to the posterior aspect of the laparotomy wound. No macroscopic liver damage was evident in any animal. The area of the partial hepatic lobectomy was often adherent to the anterior wall of the stomach. Adhesion grading revealed no significant differences between the three groups, although mean(s.d.) grades were slightly lower, in general, in the Vivostat group (2·5(0·9) *versus* 3·3(0·9) for Surgicel and 3·3(0·6) for controls; $P = 0{\cdot}06$, Kruskal–Wallis test). One animal in the Surgicel group, which had an uncomplicated postoperative recovery, had an intraperitoneal collection consisting of 10–15 ml of bile-stained fluid in the subhepatic space. There were differences between the treatment groups with regard to bile duct proliferation, presence of giant cells, calcification and eosinophilia. Vivostat-treated animals showed no difference compared with the control group with regard to bile duct proliferation; however, there was a statistically significant increase compared with Surgicel ($P < 0{\cdot}01$, Wilcoxon rank sum test). Treatment with Vivostat was also associated with a statistically significant increase in calcification ($P < 0{\cdot}05$) and eosinophilia ($P < 0{\cdot}001$) compared with both Surgicel and controls. In contrast, Surgicel-treated animals showed a statistically significant increase in the presence of giant cells compared with the other treatment groups ($P < 0{\cdot}01$ *versus* Vivostat, $P < 0{\cdot}05$ *versus* controls). There were no significant intergroup differences for any of the other parameters assessed. Mildly raised transaminase levels were noted in 11 animals before operation and in 20 animals at death. No other significant abnormality was found in clinical biochemistry. Haemoglobin and serum iron levels were generally low in all treatment groups, while the mean corpuscular volume was in the normal range.

Discussion

Liver surgery is one of the most potentially beneficial applications for haemostatic agents[6,13,14]. Obtaining a satisfactory preclinical evaluation requires a reproducible large-animal model. Partial hepatectomy in the pig is close to the human situation in that the liver is a large organ with a consistent lobular anatomy, allowing resection at a constant site. Other groups have used the porcine partial hepatectomy model for the evaluation of haemostatic agents[7,24,25]. The model is not, however, without complications and recognized causes of death unrelated to partial hepatectomy were encountered in this study, including malignant hyperpyrexia and small bowel volvulus[26]. Portal inflow occlusion is well tolerated in humans for up to 1 h[27,28]. Portal inflow occlusion is the preferred method of effecting liver vascular stasis using fibrin sealants, as a period of low vascular flow is required for cross-linkage of the fibrin polymers.

The liver resection was highly reproducible with only small variations being noted between animals with regard to the weight, circumference and surface area of resected liver, the number of major vessels requiring ligation and the duration of portal inflow occlusion. Arterial blood pressure was not routinely monitored as previous studies have shown no correlation with blood loss[24].

The mean blood loss in the first 10 min following resection in control animals was 94·3 g, which represents approximately 10 per cent of the circulating blood volume in a 20-kg pig[26]. Blood volume was corrected by colloid, but blood transfusion was not given in this study. Vivostat system-derived fibrin sealant was found to be at least as effective as Surgicel in stopping blood loss from the parenchyma, with no statistically significant difference in blood loss within the first 10 min after resection in the active treatment groups. The ease of use of these two agents was not quantified directly, but the off-the-shelf availability of Surgicel is an obvious advantage. A significant disadvantage of Surgicel, however, is that it must be removed before additional methods of haemostasis can be attempted, if control is not achieved with the first application. With Vivostat, immediate retreatment of any continued sites of bleeding is possible. In this study there were several occasions following treatment with Vivostat or Surgicel where an additional application would have been appropriate. The protocol, however, did not allow additional treatment applications until after the 10-min analysis.

The time taken to achieve haemostasis is perhaps as important as the volume of blood lost. The median time to haemostasis was significantly shorter in both the Vivostat and Surgicel treatment groups (8 and 10 min respectively) than in the untreated controls (31 min). Extrapolation of these data to human liver resection, assuming a resection surface[6] of 70 cm^2, would suggest a possible time saving of 1 h in the operating room.

The mean volume of Vivostat used to cover a resection surface of approximately 30 cm^2 was 2·3 ml. Extrapolating to human liver resection, one autologous donation of 120 ml of whole blood would produce 3–6 ml of fibrin sealant. This is likely to be sufficient to cover the average resection cross-sectional area[6] of approximately 70 cm^2. This 120 ml of blood represents less than 5 per cent of the total circulating volume and is unlikely to be of clinical significance in adults undergoing liver resection.

The recovery period and second laparotomy were included to permit assessment of secondary haemorrhage, bile leaks and adhesion formation, as well as histological assessment of the resection margins. No secondary haemorrhage was observed and bile leak was found in only one animal in the Surgicel group. This low incidence of complications is similar to that in a recent human clinical series[29]. Unfortunately, the postoperative results did not allow any conclusions to be drawn concerning the use of Vivostat for the prevention of postresection bile leaks, a major cause of morbidity and mortality in some clinical series[29–31].

Adhesions are a significant clinical problem following major abdominal surgery[31,32], and preliminary data on Vivostat suggest a possible role in the prevention of postsurgical adhesions[33–35]. Although this study was not designed specifically to evaluate adhesion formation, there was a trend to lower overall adhesion grading in the Vivostat group. Further evaluation of this potential clinical benefit is clearly required. There were, however, significant differences in the histopathological evaluation of the resection interface. Surgicel-treated animals were noted to have a significant giant cell reaction, possibly related to a foreign body response[8,10]. In contrast, Vivostat-treated animals showed evidence of bile duct proliferation, eosinophilia and calcification at the interface, which were not apparent in the control and Surgicel groups. Bile duct proliferation is a usual response to duct damage and is likely to be part of the normal regeneration process[36,37]. Further evaluation in a more controlled model is required, however, to determine whether Vivostat itself stimulates the regeneration of the cut surface. Calcification is also a normal response in wound healing. The eosinophilia seen may reflect a subclinical immunological reaction to the presence of foreign protein, as human-derived Vivostat was used in this study.

The majority of animals had low haemoglobin and iron levels both before and after operation. This was most probably dietary in aetiology and of no clinical relevance. A raised white blood count was found in some animals from each of the treatment groups 1 week after operation and occurred without clinical evidence of sepsis. This was considered to be a response to anaesthesia and the surgical procedure. Liver function tests and coagulation profiles revealed no evidence of liver failure in any animal following partial hepatic lobectomy. Increased levels of transaminases were seen in the majority of animals after operation, reflecting a degree of hepatocellular damage. This is a common finding after liver resection.

The results of this controlled randomized study demonstrate that Vivostat system-derived fibrin sealant is at least as effective as Surgicel regenerated oxidized cellulose gauze in reducing blood loss and achieving haemostasis following partial hepatectomy. Treatment with Vivostat was also associated with a trend towards reduced adhesion formation and accelerated bile duct proliferation, which merits further evaluation. Additional benefits may be realized in the clinical setting where the fibrin sealant is prepared from the patient's own blood, resulting in improved biocompatibility.

Acknowledgements

The authors thank the Comparative Biology Unit for technical assistance, Drs K. Shah and P. Sibbons (Northwick Park Institute for Medical Research) for histopathological analysis, and Caroline Dore (Department of Medical Statistics and Evaluation, Imperial College School of Medicine) for statistical analysis. This study was supported by an educational grant from ConvaTec to B.R.D. (grant no. BSB2).

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Original article

Duplex-guided thrombin injection for iatrogenic femoral artery pseudoaneurysm is effective even in anticoagulated patients

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Background: The aim was to evaluate the efficacy and safety of percutaneous thrombin injection as an alternative non-operative method for treating postcatheterization femoral artery pseudoaneurysm in both anticoagulated and non-anticoagulated patients.

Methods: Thirty consecutive patients with a femoral artery pseudoaneurysm secondary to radiological catheterization confirmed by duplex imaging were included. Thrombin 200–2000 units (1000 units/ml) in a titrating dose was injected into the centre of the cavity under duplex ultrasonographic guidance. Thrombosis was assessed in real time using B mode and colour flow. No sedation or anaesthesia was required during the procedure. The distal pulses and ankle pressures were evaluated before and immediately after the injection, to exclude propagation of thrombus into the femoral artery.

Results: Successful rapid thrombosis of the false cavity was induced in all 30 patients. There were no immediate or mid-term procedure-related complications, or recurrences at 6 weeks. Eighteen patients were anticoagulated therapeutically at the time and following the procedure with either heparin or warfarin.

Conclusion: Percutaneous thrombin injection is a simple, quick, painless, safe and effective technique, particularly in patients taking anticoagulants.

Paper accepted 26 December 1999

British Journal of Surgery 2000, 87, 796–801

Introduction

The femoral artery remains the most popular peripheral site for radiological catheter access. As larger catheters are used for stenting and endovascular grafting, the incidence of iatrogenic pseudoaneurysm is becoming as high as 1–2 per cent[1–4]. The increased use of anticoagulants following interventional procedures has also been implicated in the rising incidence of false aneurysms at the puncture site. The treatment of this complication has traditionally involved observation, surgical repair or, more recently, ultrasonographically guided compression repair (UGCR). Since the latter was first reported by Fellmeth *et al.*[5] in 1991, the success rate has ranged from 33 to 95 per cent, depending on factors such as the size, site and age of the false aneurysm, the number of treatments attempted and the presence of concurrent anticoagulation[5–12]. Although UGCR is widely used as the first method of treatment, the results are variable and the procedure is time consuming and painful. Surgical repair carries a significant risk of both wound infection and lymphatic leak and, compared with compression, requires prolonged hospitalization and higher costs.

This study evaluated the safety and efficacy of an alternative technique described recently by Liau *et al.*[13] and Kang *et al.*[14] in both anticoagulated and non-anticoagulated patients. The aim was to determine the appropriate dose of thrombin required to induce rapid thrombosis when injected directly into the pseudoaneurysm cavity under duplex ultrasonographic guidance.

Patients and methods

Thirty consecutive patients with a clinically suspected femoral artery pseudoaneurysm following cardiac and peripheral arterial catheterization were referred to the vascular laboratory for duplex ultrasonographic assessment. A 6-Fr sheath was used in patients undergoing a diagnostic radiology procedure whereas those having therapeutic balloon angioplasty or stent insertion required a sheath of at least 8 Fr. The demographic details of the patients together with the indications for angiography and data relating to the pseudoaneurysm cavities are shown in *Table 1*. Duplex ultrasonography was performed with an ATL HDI 3000 (4–7-MHz linear array transducer;

Advanced Technology Laboratory, Bothell, Washington, USA). The pseudoaneurysm and associated defect in the underlying native artery were assessed in both transverse and longitudinal planes (*Fig. 1a*). Measurements of the false cavity were calculated in three dimensions, in addition to the length and size of the communicating tract and depth of the cavity centre from the skin surface. Patency of the distal vessels was also determined by duplex imaging, and by palpation of the distal pulses and measurement of the ankle : brachial pressure index. The level of anticoagulation was measured before treatment (*Table 2*). All patients proceeded to thrombin injection, regardless of the level of systemic anticoagulation, and without reversal of their anticoagulation before the procedure. Platelet activity was

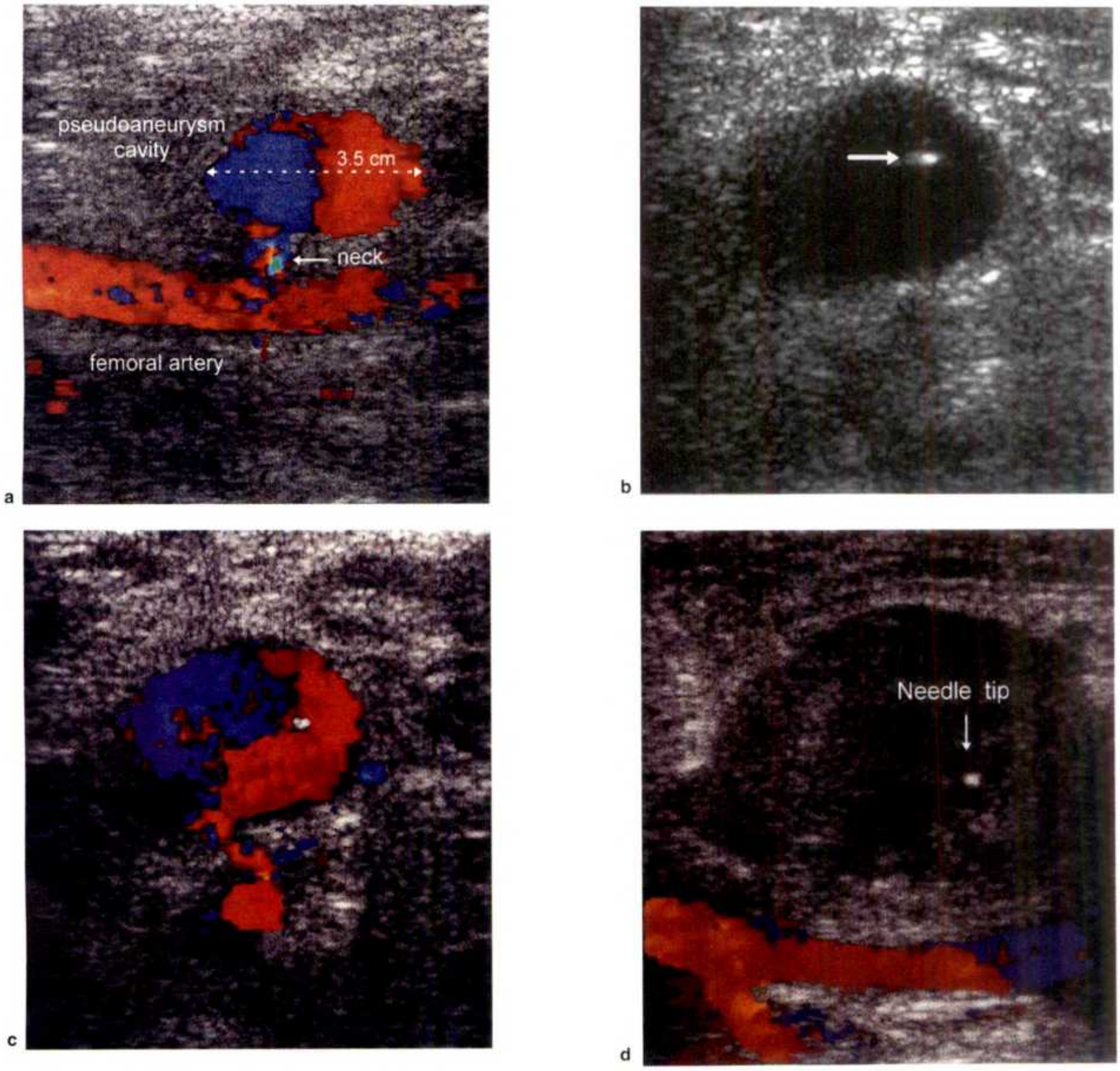

Fig. 1 **a** Duplex ultrasonographic image of an pseudoaneurysm, demonstrating arterial flow through a long narrow neck arising from the defect in the femoral artery and turbulent colour flow into the large false cavity.

b B-mode image of the needle placed under duplex guidance into the centre of the pseudoaneurysm cavity. The arrow indicates echogenic thrombus that forms at the tip of the needle, which assists accurate positioning.

c Colour flow is recommenced during the slow injection of thrombin as it is titrated to the real-time development of thrombosis within the false cavity.

d Following successful thrombosis of the pseudoaneurysm, the femoral vessels are assessed for patency and flow to exclude any distal spillage of thrombin into the native circulation

Table 1 Demographic details of 30 patients with an iatrogenic femoral artery pseudoaneurysm

Age (years)*	65 (60–75)
Sex ratio (M : F)	13 : 17
Time after angiogram (days)†	7 (2–90)
Procedure	
Diagnostic	17
Therapeutic (angioplasty/stent)	13
Site of origin	
Common femoral	15
Superficial femoral	9
Profunda femoris	6
Communicating tract length (cm)*	1·2 (0·7–1·8)
Maximum cavity diameter (cm)†	3 (2·2–8·0)
Multilocular	8

Values are median *(interquartile range) or †(range)

Table 2 Anticoagulation status and relevant laboratory findings in 30 patients with a femoral pseudoaneurysm before undergoing thrombin treatment

	No. of patients	Coagulation data	
	(*n* = 30)	APTT (s)	INR
Anticoagulated	18		
Heparin			
Unfractionated	8	82 (69–88)	
Low molecular weight	6	52 (35–60)	
Warfarin	4		2·3 (2·1–2·6)
Non-anticoagulated	12	38 (32–48)	1·1 (1·0–1·3)

Values are median (interquartile range). APTT, activated partial thromboplastin time (normal range 28–43 s); INR, international normalized ratio (normal value 0·9–1·2)

not studied in patients taking antiplatelet medication and these patients were not considered to be clinically anticoagulated at the time of diagnosis and treatment, nor were those given heparin only at the time of the angiographic procedure.

Duplex-guided technique

Following informed consent, all patients with a false aneurysm greater than 2 cm in diameter and an otherwise normal arterial circulation were included in the treatment protocol. Patients were excluded if there was evidence of active infection in the groin, a large haematoma causing impending skin necrosis or lower limb ischaemia with poor run-off vessels. Patients with a large defect in the artery wall on duplex imaging (greater than 2 mm in length or without Doppler and colour flow evidence of raised velocities indicating a small neck and 'jet' of flow into the pseudoaneurysm) were also deemed unsuitable for thrombin injection because of the potential risk of distal embolization.

Bovine thrombin (1000 US units/ml; GenTrac Inc., Middleton, WI, USA) in powdered form was reconstituted with 5 ml sterile normal saline and drawn into a 2-ml syringe using a 22-G needle. Under aseptic conditions, with continuous real-time B-mode ultrasonographic imaging, the probe was placed transversely over the pseudoaneurysm. The needle was inserted into the centre of the cavity under duplex control, with a small amount of echogenic thrombus at the needle tip helping to confirm correct needle placement before injection (*Fig. 1b*). With the needle maintained in position, colour flow was used to assess flow within the sac (*Fig. 1c*), and without any superficial compression thrombin was injected slowly at a titrating dose up to a total of 2000 units (2 ml). Usually, within a few seconds, there was a flash of colour as the thrombin reacted with the flowing blood, and complete thrombosis was confirmed by visualizing echogenic thrombus together with loss of flow within the cavity (*Fig. 1d*). Multiloculated pseudoaneurysms (*Fig. 2*) were treated by injection of thrombin into the deeper cavity (nearer to the puncture site) using a longer spinal needle. This resulted in

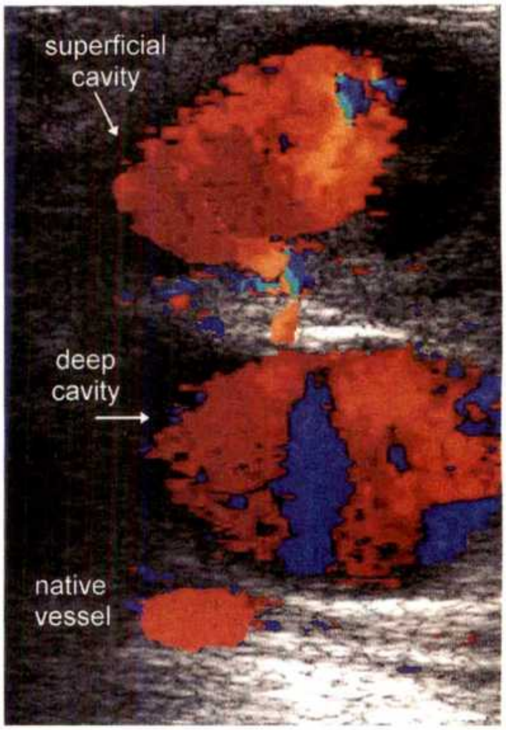

Fig. 2 Multiloculated femoral artery pseudoaneurysm with a small channel connecting the two cavities. This was treated successfully with thrombin injection into the deeper cavity with subsequent spontaneous thrombosis of the more superficial cavity

spontaneous thrombosis in the more superficial cavities without the need for either compression or further injection.

After treatment, the pedal pulses were again palpated and the Doppler ankle pressure checked to exclude any distal thrombotic propagation. The patients underwent repeat imaging after 24 h to exclude any recurrence before discharge from hospital. Clinical and duplex follow-up at 6 weeks was performed to monitor regression of the residual subcutaneous haematoma and to exclude late recurrence.

Statistical analysis

Comparison between the anticoagulated and non-anticoagulated patients was performed using the Mann–Whitney ranking test for unpaired data.

Results

Duplex-guided thrombin injection successfully induced thrombosis in all 30 pseudoaneurysms regardless of the anticoagulation status of the patient. In 26 patients complete thrombosis occurred within 20 s of the initial injection; in the other four there was incomplete thrombosis and a small rim of arterial flow in the periphery of the cavity persisted for up to 2 min. All of these pseudoaneurysms were treated with more than 1000 units of thrombin and subsequently thrombosed spontaneously without the need for either superficial compression or further thrombin injection. Two of these patients were anticoagulated (one with warfarin, one with heparin); however, the false cavities in these patients were less than the median size of 3 cm in diameter (*Table 1*).

The level of anticoagulation was in the therapeutic range in patients on unfractionated heparin or warfarin. Patients on low molecular weight heparin (enoxaparin 60–80 mg/day) did not have anti-Xa levels measured, but were prescribed standard treatment rather than prophylactic doses. In addition, four patients were taking ticlopidine 500 mg, which has been shown to impair platelet function and is associated with bleeding complications[15].

The median titrated dose of thrombin administered was 500 (range 200–2000) units. However, in the later cases, a much smaller initial dose was injected with successful results (250–500 units). There was no significant difference between the size or age of the pseudoaneurysm in the anticoagulated and non-anticoagulated patients.

There were no immediate or mid-term complications related to the procedure, such as allergy to bovine thrombin. No recurrences were detected the day after treatment or at the 6-week follow-up. The distal pulses and ankle pressures were unchanged in all patients with no evidence of native vessel thrombosis secondary to thrombin spillage. One patient died 1 week following successful treatment of the pseudoaneurysm from complications related to poor ventricular function associated with revisional coronary artery surgery.

No patient required either analgesia or sedation; the entire procedure was completed within 10 min and was well tolerated by all patients. As all pseudoaneurysms thrombosed following a single thrombin injection, no factor was identified that predicted either success or failure. The procedure was equally effective in both large and small sacs, acute and chronic lesions, unilocular and multilocular cavities, and, most importantly, in patients who were therapeutically anticoagulated. Patients were fit for discharge the following day unless their cardiac management precluded this. In the future, this could be an outpatient procedure.

Although the majority of patients were diagnosed and treated within the same hospital admission, five were admitted at least 4 weeks after angiography with a painful pulsatile groin mass in the absence of any localized bruising. One patient with an 8-cm pseudoaneurysm developed paraesthesia related to compression of the femoral nerve.

Discussion

More therapeutic angiographic procedures are being performed. Potent antithrombotic and anticoagulation therapy is widely administered to prevent stent/vessel occlusion. As a result, the incidence of postcatheterization puncture site complications has increased. The majority of large, symptomatic pseudoaneurysms require intervention to prevent the complications of rupture or progressive enlargement[2,16–19]. However, the treatment of smaller lesions is less clear. Some recommend conservative monitoring of selected postcatheterization injuries including arteriovenous fistula[3,20]. In the present study, half of the patients treated had a false aneurysm greater than 3 cm in diameter, and none had an aneurysm smaller than 2 cm. The majority of patients were anticoagulated, and all were symptomatic and would have been excluded from conservative monitoring. While treatment of very small false aneurysms is not advocated here (this is the only duplex criterion associated with spontaneous resolution[20, 21]), the ease, speed, safety and efficacy of thrombin injection make it an attractive option for most patients presenting with this complication.

Although UGCR has surpassed surgical repair as the first-line treatment of femoral pseudoaneurysms, it has significant limitations. There are lower initial success rates and significant early recurrence in long-standing and large pseudoaneurysms, particularly in patients taking anticoagulants[5–12]. Some reports, however, indicate that anticoagulation does not significantly impair results, provided that accurate probe placement and multiple treatments lasting up to several hours can be accomplished[9,22]. This is poorly tolerated by patients with a pseudoaneurysm that is well established and difficult to compress. In some cases the pressure required to compress a false cavity also occludes the underlying artery and has been associated with either local arterial thrombosis or distal embolization[5].

The use of thrombin for the treatment of peripheral arterial pseudoaneurysm was reported using fluoroscopic guidance techniques by Cope and Zeit[23] in 1986 and Walker *et al.*[24] in 1987. The use of thrombin in the treatment of femoral artery pseudoaneurysm under duplex guidance has also been reported. Kang *et al.*[14] proposed the method adopted in the present series, of direct puncture under guidance into the centre of the cavity assisted by the visualization of echogenic thrombus at the tip of the needle. Provided that a volume of thrombin solution well below the total volume of the cavity is administered, it is unlikely to be forced into the native circulation and cause distal thrombotic complications. The largest volume used in this series was 2 ml, considerably less than the cavity volumes being treated. The authors now believe that less thrombin is required to induce adequate thrombosis in pseudoaneurysms of all sizes, even if the patient is anticoagulated.

Other investigators have suggested alternative techniques to visualize the cannula administering the thrombin and to arrest blood flow into the cavity. Micro-air bubbles in saline injected through the cannula[13] appear to be unnecessary provided that some thrombin solution is present in the bevel of the needle to form a small thrombus which is visible on duplex imaging. Aspiration into the hub of the needle on insertion into the pseudoaneurysm cavity is not necessary to confirm the position and could result in occlusion of the needle with acute clot, making subsequent injection impossible. Concern over spillage into the native artery has led other investigators to compress the false aneurysm cavity before injection to prevent blood flow into it during the injection[26]. This makes accurate positioning of the needle difficult and is unnecessary. Others have placed an inflated angioplasty balloon at the site of the arterial defect, but this is more invasive and costly[27].

A complication that required intervention, related to distal thrombosis when treating a large brachial artery pseudoaneurysm, has been encountered in a young baby in this unit[28]. Although the outcome was favourable, the hazards in the small brachial artery, where the neck of the sac may be shorter owing to less subcutaneous fat, suggest that thrombin injection should be used with caution.

In conclusion, thrombin injection should now be regarded as first-line treatment in all patients with a femoral pseudoaneurysm that warrants intervention, regardless of the anticoagulation status. Furthermore, chronic pseudoaneurysms (such as those in the five patients with false aneurysms older than 4 weeks), or those arising posteriorly from the profunda femoral artery which are difficult to compress can be treated with similar efficacy by accurate duplex-guided injection of thrombin. Surgical intervention is indicated only in patients due to have a planned procedure in the groin or those in whom a large haematoma requires drainage to prevent local complications.

Acknowledgements

The authors acknowledge the assistance given by Mr Gerrard Stansby, Mr John Wolfe, Professor Averil Mansfield and Mr David Nott in the treatment of their patients, and the technical advice given by Dr Steven Kang and Dr Nicos Labropoulos from the Department of Surgery, Loyola University, Maywood, IL, USA.

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Original article

Functional outcome after restorative panproctocolectomy for ulcerative colitis decreases an otherwise enhanced quality of life

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Background: Restorative panproctocolectomy is a favoured operation for ulcerative colitis, but altered bowel habit may adversely affect overall quality of life.
Methods: Specific and generic quality of life questionnaires and an instrument to award money for continuing disability based on government guidelines were sent to 103 patients who had curative surgery for ulcerative colitis between 1995 and 1997. Seventy-one patients returned completed questionnaires: 30 with an ileostomy (representing incontinence and abnormal body image), 11 with a Koch pouch (representing continence and abnormal body image) and 30 with a pelvic pouch (representing continence and normal body image).
Results: Patients valued the disability of having an ileostomy similar to that for a Koch pouch or a pelvic pouch: £40 000, £30 000 and £40 000 respectively ($P = 0{\cdot}97$). There was no sex difference. Body image measured with a visual analogue scale (least = 1, worst = 10) was worst with the ileostomy and Koch pouch (8 each) and best with a pelvic pouch (5) ($P = 0{\cdot}06$). However, pelvic pouches scored significantly worse than an ileostomy with regard to altered bowel emptying (pelvic pouch, 8; Koch pouch, 7; ileostomy, 5) ($P = 0{\cdot}01$).
Conclusion: Poor function after pelvic pouch surgery offsets any advantage in body image over an ileostomy. Thus, overall quality of life and perceived monetary damage were the same for the two operations. Improved pelvic pouch function is likely to be reflected in better quality of life after restorative panproctocolectomy.

Presented to the British Society of Gastroenterology, Glasgow, UK, March 1999, and published in abstract form as *Gut* 1999; 44(Suppl 1): A414
Paper accepted 28 November 1999
British Journal of Surgery 2000, 87, 802–807

Introduction

Restorative proctocolectomy with an ileal reservoir has emerged as the procedure of choice in ulcerative colitis because it preserves body image, eliminates the risk of cancer and restores anal defaecation. In spite of this, an unresolved conflict of opinion persists in the literature. While some publications suggest that quality of life with a pelvic pouch is better than that with a continent or Brooke ileostomy[1–3], others have shown that, regardless of the type of operation performed, patients express satisfaction with all three procedures due to eradication of the disease[4–7]. However, all concerned concede that the avoidance of an abdominal stoma by the pelvic pouch procedure grants the individual additional benefit through enhancing quality of life. What is less certain is whether the associated alteration of bowel emptying, considered as an index of functional outcome, confers any significant advantage over the method of faecal expulsion via a conventional or continent ileostomy.

In this study, an attempt was made to measure patient perception of well-being after surgery for ulcerative colitis. A simple innovative assessment of disease-specific drawbacks has enabled evaluation of outcome as well as the impact of altered bowel habit on overall patient quality of life.

Patients and methods

Informed consent was obtained from patients included in the study. One hundred and three patients who had undergone surgery for ulcerative colitis between 1995 and 1997 were sent an in-house questionnaire designed specifically to measure seven selected items (body image, altered bowel emptying, diet, odour, clothing, noise and sexual relationship) perceived by patients as drawbacks of surgery (proxy of quality of life). At the time of initial operation all patients were fully informed and had selected their respective operative procedure.

Seventy-one completed questionnaires were returned (70 per cent response rate) from 31 men and 40 women (mean age 43 (range 22–71) years, mean duration of follow-up 13 (range 8–34) months), comprising three groups: Koch pouch, 11 patients; ileostomy, 30 patients; and pelvic pouch, 30 patients. Three simple concepts – (a) financial compensation, (b) rank order of problems (1–7, where 1 corresponded to least and 7 the worst problem) to reflect their relative importance, and (c) a visual analogue scale (VAS) (1–10, where 1 corresponded to the least problem and 10 to the worst) to indicate absolute importance of these items – were adopted in the construction of this quality-of-life measure in addition to the standard validated Short Form (SF)-36 questionnaire.

Monetary award

Patients were asked to consider an imaginary case of accidental injury where there had been no attributable fault whatsoever, and to award a sum of money to a third party (same age and sex as themselves) for the continuing disability of living with a Koch pouch, ileostomy or pelvic pouch. It was assumed that the third party had already been compensated for the original injury and operation, and was perfectly happy with this level of compensation. The awards were a reflection of suggested government guidelines for compensation in personal injury cases[8], which ranged from £6000 for minor facial scarring (can hide with makeup) to £130 000 for quadriplegia. All awards had income tax implications (a proportional rise for those in employment and a corresponding reduction in benefits for those not in paid employment) to guard against excessive compensation.

Visual analogue scale

Each of the seven items was ranked on the VAS (1–10) such that 1 indicated the least and 10 the greatest problem. Of the 30 patients who had a pelvic pouch, 23 had undergone a staged procedure with the formation of a temporary ileostomy, but none was converted from a pouch to a permanent ileostomy. Patients in this group were asked to complete a second VAS for each of the seven items, given the hypothetical situation in which it had not been possible to construct a pelvic pouch and the only option was a permanent ileostomy.

Short Form-36 questionnaire

The validated standard SF-36 questionnaire for assessing global quality of life was administered to all patients.

Statistical analysis

For comparison of two independent group medians the Mann–Whitney *U* test was used, and Kruskal–Wallis one-way analysis of variance of the ranks for comparison of more than two independent group medians. For paired comparisons from individuals in the subgroup of patients with a pelvic pouch, a Wilcoxon matched-pairs signed-rank sum test was performed. Spearman rank correlation coefficient was calculated to relate compensation values with each quality-of-life measure. $P < 0{\cdot}05$ was considered significant.

Results

Compensation value

In this section there were 60 observations in 36 women and 24 men (11 observations were incomplete and these patients were excluded). The median monetary award did not differ significantly with sex (women £37 500 (95 per cent confidence interval (c.i.) £20 000–47 092), men £35 000 (95 per cent c.i. £14 494–50 000); $P = 0{\cdot}97$, Mann–Whitney *U* test) or type of operation performed (ileostomy £40 000 (95 per cent c.i. £22 260–50 000), Koch pouch £30 000 (95 per cent c.i. £15 978–50 000), pelvic pouch £40 000 (95 per cent c.i. £12 619–50 000); $P = 0{\cdot}97$, Kruskal–Wallis ANOVA). The median monetary award did not differ significantly between the six combinations of group and sex ($P = 0{\cdot}3$) (*Table 1*), nor for the following categories: those who thought the opposite sex should receive less, the same or more ($P = 0{\cdot}18$), whether compensation should depend on age ($P = 0{\cdot}16$) and between those who thought a younger

Table 1 Hypothetical monetary compensation for sex and type of operation

	Median value (£)			
	End ileostomy	Koch pouch	Pelvic pouch	*P*
All patients	40 000	30 000	40 000	0·97*
Men	45 000	30 000	20 000	
Women	26 000	28 000	50 000	0·30†

*Kruskal–Wallis ANOVA; †Mann–Whitney *U* test person should receive less or more ($P = 0{\cdot}31$). There was no significant correlation between compensation value and each of the seven items (proxy of quality of life) on the rank order scale using the Spearman correlation. However, on the VAS there was significant positive correlation for body image ($r_s = 0{\cdot}3$, $P = 0{\cdot}02$), altered bowel emptying ($r_s = 0{\cdot}31$, $P = 0{\cdot}02$) and diet ($r_s = 0{\cdot}28$, $P = 0{\cdot}03$). There was significant negative correlation between the amount of money awarded and only two domains (social functioning ($r_s = -0{\cdot}30$, $P = 0{\cdot}02$) and body pain ($r_s = -0{\cdot}34$, $P = 0{\cdot}009$)) on the SF-36 scale.

Rank order

Seventy-one observations (30 ileostomy, 11 Koch pouch, 30 pelvic pouch) were evaluated for rank order, VAS score and SF-36. There was no significant difference in the median ranking of the type of operation performed for five patient concerns (odour, noise, clothes, diet and sexual relationship; P not significant, Kruskal–Wallis ANOVA), but significant differences were demonstrated for body image ($P = 0{\cdot}01$) and altered bowel emptying ($P = 0{\cdot}002$) (*Table 2*).

Visual analogue scale

The median ranking of the three surgical procedures was not significantly different for five patient concerns (body image, odour, noise, clothes and sexual relationship; P not significant, Kruskal–Wallis ANOVA), but this was not the case for diet ($P = 0{\cdot}02$) and altered bowel emptying ($P = 0{\cdot}01$) (*Table 3*).

In the 23 patients with a pelvic pouch who had a staged procedure, a median ranking on the VAS was compared for pelvic pouch and ileostomy (hypothetical situation). There were significant differences for all the variables except one (*Fig. 1*). For six of seven patient concerns, there was significant improvement with the pelvic pouch ($P < 0{\cdot}05$, Wilcoxon test).

Short Form-36

No significant difference was demonstrated between the three operative groups in any of the eight domains of the SF-36 (*Table 4*).

Discussion

It is generally assumed that quality of life with an ileal pelvic pouch is better than that with a Brooke or continent ileostomy, because a stoma and faecal incontinence are avoided. However, this remains an assumption without proof. It is possible that surgical eradication of the disease, the absence of a sufficiently sensitive evaluating instrument[5] and suggestions that different domains of quality of life are differentially influenced by the type of operation performed[9] might explain why this is so. Despite this lack of evidence and associated morbidity due to pelvic sepsis and pouchitis, most patients who require surgical intervention for ulcerative colitis prefer the pelvic pouch procedure[10,11]. The perceived benefits appear to be, first, the preservation of body image and, second, the anticipated superior functional outcome.

This study was designed to assess patient quality of life and the effect of altered bowel emptying in a group of matched subjects (disease, age and sex) who had undergone one of three curative procedures for ulcerative colitis. A preliminary outpatient study had identified seven of the most frequent patient concerns following operation. These drawbacks (proxy of quality of life) were measured using rank order and VAS, which formed the basis of a unique in-house disease-specific quality-of-life tool which was not

Table 2 Effect of type of operation on ranking (1–7) of seven quality-of-life problems

	Median rank*			
Problem	Ileostomy	Koch pouch	Pelvic pouch	P†
Body image	4	6	3	0·01
Altered bowel emptying	4	5	7	0·002
Odour	5	4	5	0·57
Noise	4	3	5	0·07
Sexual relationship	4	4	4	0·94
Clothes	2	2	1·5	0·82
Diet	2	4	3·5	0·06

*1 = least, 7 = worst problem. †Kruskal–Wallis one-way analysis of variance

Table 3 Effect of type of operation on the visual analogue scale (1–10) for seven quality-of-life problems

	Median score*			
Problem	Ileostomy	Koch pouch	Pelvic pouch	P†
Body image	8	8	5	0·06
Altered bowel emptying	5	7	8	0·01
Odour	8	6	5	0·20
Noise	6	6	5·5	0·61
Sexual relationship	7	5	5	0·69
Clothes	3	1	3·5	0·82
Diet	2	5	5·5	0·02

*1 = least, 10 = worst problem. †Kruskal–Wallis one-way analysis of variance

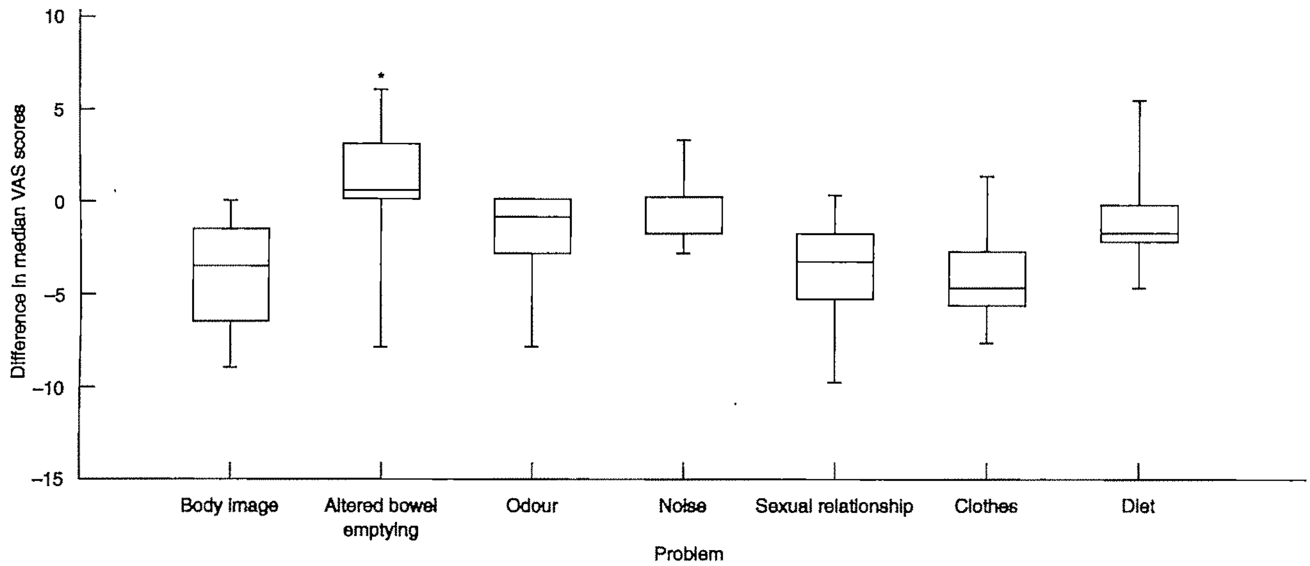

Fig. 1 Comparison of visual analogue scale (VAS) scores between a hypothetical permanent ileostomy and pelvic pouch in 23 patients who had a staged pelvic pouch operation. $^*P = 0{\cdot}11$; all other differences were significant ($P < 0{\cdot}05$, Wilcoxon test)

Table 4 Effect of type of operation on the SF-36

	Median score			
Problem	Ileostomy	Koch pouch	Pelvic pouch	P^*
Health perception	55	70	57	0·16
Physical functioning	80	90	90	0·26
Role limit – physical	75	100	88	0·64
Role limit – emotional	100	100	100	0·70
Social functioning	88	88	88	0·90
Mental health	76	84	68	0·12
Bodily pain	80	100	90	0·14
Energy/fatigue	53	65	43	0·18

*Kruskal–Wallis one-way analysis of variance

only relevant but a useful index of surgical outcome. In addition, a validated global questionnaire (SF-36) was administered to all patients in the belief that combining a general and disease-specific instrument on one scale would yield the best of two worlds.

For 60 observations, the compensation value for residual quality of life did not differ significantly for sex, age or type of operation performed. This supports the findings of previous studies which have demonstrated that patient well-being is equivalent for all three techniques[4–7]. There was no correlation between compensation value and patient concerns on the rank order scale, which is not surprising as this tool measures the relative importance of these drawbacks and as such is liable to variation. However, there was significant positive correlation between compensation value and three drawbacks on the VAS (body image, altered bowel emptying and diet), and negative correlation in two domains of the SF-36 scale (social functioning and bodily pain). These findings suggest that the compensation value model is a useful indicator of changes in these areas, representing patient perception of quality of life.

Some investigators employing disease-specific non-validated quality-of-life measures have shown that function after an ileal pelvic pouch procedure is superior to that following ileostomy[2,12]. Others claim that long-term functional outcome does not deteriorate with time, is satisfactory and comparable to results in a control group undergoing cholecystectomy[13–16]. In these studies overall functional score was the summation of subscores, allowing those areas where function had improved to compensate for other shortcomings.

In the present study, the various components of function were grouped under a common denominator (alteration of bowel habit) and assessed accordingly. The revelation that the functional outcome with a pelvic pouch was significantly worse than with a continent or Brooke ileostomy on the rank order and VAS was unexpected, even though concerns regarding body image were expectedly better. Remarkably, a similar pattern evolved in the pelvic pouch subgroup of patients who had experienced a temporary ileostomy, for whom there were significant improvements in all areas, with the exception of function. It is noteworthy that participants in this study were selected at random from the hospital database, which negates the possibility that this difference in the data may have been attributable to a disgruntled minority of patients with a pelvic pouch and poor functional outcome after operation for ulcerative colitis. In addition, data presented here concur with the observations of others[5,7] that generic instruments seem to be unhelpful in attempts to distinguish overall quality of well-being for the three procedures.

The retrospective nature of this study, the relatively short follow-up of patients and the use of a non-validated tool for quality-of-life assessment are recognized limitations. However, prospective randomized trials of these techniques are difficult to conduct. The Koch pouch is associated with increased morbidity and should no longer be performed routinely, and there is now a certain imbalance among patients in favour of pelvic pouch surgery over ileostomy. Although relatively short, there was no significant difference in the mean follow-up of the three groups. Furthermore, a validated disease-specific tool for measuring quality of well-being after curative surgery is not in existence.

There is no doubt that quality-of-life assessment is an important outcome measure because it highlights the need for continued refinement of surgical technique and management strategies. A clear and important deduction to be drawn from this study is that the functional outcome after restorative panproctocolectomy may not be as good as first thought and contributes to a reduction in an otherwise improved quality of life. To date, attempts to improve pelvic pouch function by modifying its design have produced mixed results. While some reports claim that increased pouch capacity improves functional outcome[17,18], others refute this[19,20]. Recently, studies have shown that topical phenylephrine (an α-adrenergic agonist) increases resting anal sphincter pressure in healthy volunteers[21]. It is conceivable that agents which selectively augment anal sphincter tone might have a useful role in improving pelvic pouch function.

Acknowledgements

The authors thank Caroline Doré for statistical advice, and also Celia Myers, Stoma Care, St Mark's Hospital. A.O'B. is supported by a grant from St Mark's Hospital/Northwick Park Institute for Medical Research, and from Dansac.

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Immunoglobulin G and albumin levels in whole gut lavage fluid provide an objective measure of pouch ileitis

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Background: Gut protein loss is a characteristic of inflammatory bowel disease (IBD), and immunoglobulin (Ig) G, albumin and α_1-antitrypsin concentrations in whole gut lavage fluid (WGLF) correlate with clinical disease activity. If inflammation in ileoanal pouches is similar to IBD, then measurement of protein-losing enteropathy by analysis of WGLF may provide an objective assessment of disease activity in pouches.

Methods: Forty-two patients who had restorative proctocolectomy for ulcerative colitis underwent whole gut lavage with a polyethylene glycol–electrolyte solution. The first clear effluent was filtered, processed by the addition of protease inhibitors and stored at −70°C. IgG, albumin and α_1-antitrypsin were assayed in WGLF. The Pouchitis Disease Activity Index (PDAI) was calculated after pouchoscopy and biopsy; the Moskowitz criteria for pouchitis were also applied.

Results: There was a significant correlation of the pouchoscopy score and the PDAI with the concentration of WGLF IgG. All patients with 'pouchitis' according to the Moskowitz criteria had a WGLF IgG concentration greater than 10 μg/ml. The WGLF albumin level also showed a significant correlation with the PDAI, but α_1-antitrypsin concentration did not.

Conclusion: Analysis of WGLF for IgG and albumin may be useful in the assessment of disease activity in pouch inflammation.

Presented to the Surgical Research Society, Oxford, UK, January 1996 and published in abstract form as *Br J Surg* 1996; 83: 693

Paper accepted 10 December 1999

British Journal of Surgery 2000, 87, 808–813

Introduction

Pouchitis occurs in up to 30 per cent of patients who have had restorative proctocolectomy for ulcerative colitis[1]. The pathogenesis is unknown, but several hypotheses have been forwarded: a decrease in the level of luminal short-chain fatty acids, which are produced by bacteria and are trophic for the pouch mucosa[2]; a disturbance in bile acid metabolism[3]; and ischaemia of pouch mucosa[4]. It also has been proposed that pouchitis is a form of inflammatory bowel disease (IBD)[5]. This remanifestation of IBD is suggested by the finding of similar inflammatory mediators, cytokines and macrophage subpopulations in pouchitis and in IBD[6,7].

Whole gut lavage using a polyethylene glycol–electrolyte solution has been used to study intestinal immunity and inflammation[8]. The clear fluid obtained after complete cleansing of the gut is a perfusate, and previous studies in patients with IBD have shown that clinical disease activity (e.g. Crohn's Disease Activity Index (CDAI)) correlates with whole gut lavage fluid (WGLF) concentrations of albumin, α_1-antitrypsin and especially immunoglobulin (Ig) G[8,9]. Normal and actively inflamed gut can be readily differentiated by these protein concentrations in WGLF[10].

The aim of this study was to determine whether WGLF protein concentrations could be used objectively to assess the inflammatory activity in patients with pouchitis.

Patients and methods

Fifty-six consecutive patients (32 men, 24 women) aged between 18 and 75 (median 43) years were recruited between October 1994 and March 1996. All patients had had restorative proctocolectomy for ulcerative colitis. Fourteen patients were receiving metronidazole at the time of the study. Two patients had active pouchitis and had been

Table 1 Comparison of whole gut lavage fluid parameters in patients with a low and a high Pouchitis Disease Activity Index

WGLF parameter	PDAI < 7 (n = 35)	PDAI ≥ 7 (n = 7)	P*
IgG (μg/ml)	3 (1–16)	20 (1–69)	0·003
Albumin (μg/ml)	8 (3–26)	29 (12–69)	0·001
α_1-Antitrypsin (μg/ml)	3 (1–44)	8 (4–32)	0·002

Values are median (range). A Pouchitis Disease Activity Index (PDAI) of 7 or more signifies pouchitis[13]. Ig, immunoglobulin G; WGLF, whole gut lavage fluid. *Mann–Whitney *U* test

on high doses of metronidazole for 2 and 3 days before the study. The remaining 12 patients had recurrent attacks of pouchitis and had been receiving low-dose metronidazole (median 400 (range 200–800) mg daily) for more than 2 months. Since metronidazole is the standard treatment for pouch ileitis, these 14 patients were excluded from further analysis; consequently 42 patients were analysed. The period of time between the study and the creation of a functioning pouch (i.e. in continuity with the faecal stream) ranged from 6·5 to 83·7 (median 32·8 (95 per cent confidence interval (c.i.) 26·8–38·8)) months after operation. Nine patients had a W pouch, one patient had an S pouch, and the rest had J pouches. All but two patients had a stapled ileoanal anastomosis.

Before whole gut lavage, the medical history was obtained with the help of a prestructured questionnaire. After complete lavage, pouchoscopy and biopsy were performed. Pouch function was assessed according to the Öresland criteria[11].

Whole gut lavage

Patients consumed orally an isotonic polyethylene glycol–electrolyte solution (Klean-Prep; Headington, Oxford, UK) at the rate of 1 litre per h, supervised by an experienced nurse, as described previously[8]. Once the faecal effluent becomes clear, the concentration of immunoglobulins in WGLF remains stable over time[9]. The first clear specimen was filtered and processed immediately with protease inhibitors[10] and stored at − 70°C.

WGLF IgG concentration was measured by an enzyme-linked immunoassay using affinity-purified goat antihuman IgG, Fc specific (I-2136; Sigma, Aldrich Ltd, Poole, Dorset, UK)[8]. The WGLF albumin and α_1-antitrypsin levels were measured by immunoturbimetry[10]. In healthy volunteers and in patients with immunologically normal intestine, the WGLF IgG concentration is less than 10 μg/ml[8,10]; in patients with active IBD (e.g. CDAI greater than 200) the WGLF IgG concentration is above 10 μg/ml[8,10]. Similar observations have been made in patients with an ileostomy with clinically active or inactive disease[12]. A concentration of WGLF albumin greater than 26 μg/ml indicates active gut inflammation[10]. A WGLF α_1-antitrypsin concentration greater than 19 μg/ml also indicates active gut inflammation[10].

Pouchoscopy and biopsy

Rigid (17 patients, 40 per cent) or flexible (25 patients, 60 per cent) pouchoscopy was performed. The presence of oedema, granularity, friability, loss of vascular pattern, mucous exudate and ulceration was noted, each characteristic acquiring one point if present (pouchoscopy score 0–6)[13,14]. Multiple biopsies (up to three) were taken from the most inflamed area. In the absence of overt inflammation, representative biopsies were obtained approximately 10 cm from the anal verge[15]. In this area, according to Shepherd *et al.*[15], the histological findings of inflammation are expected to be most severe.

Biopsy neutrophilia, ulceration, chronic inflammation and villous atrophy were scored as mild, moderate or severe[16]. The Pouchitis Disease Activity Index (PDAI) was calculated according to the description of Sandborn *et al.*[13]. Ileoanal pouches were described according to the Moskowitz criteria of pouchitis as 'positive' or 'negative'[14].

The medicine subcommittee of Lothian Area's ethics of research committee approved the study protocol.

Statistical analysis

The data are presented as median (range and/or 95 per cent c.i). Comparisons between groups were made using a non-parametric Mann–Whitney *U* test. Correlations were performed with the Spearman coefficient. Frequencies were compared with the χ^2 test with Yates' correction. $P < 0·05$ was considered statistically significant. The Bonferroni correction was used for multiple testing between mild, moderate and severe groups.

Results

Apart from transient nausea, no serious side-effects were noted during whole gut lavage. Two patients required orogastric tube insertion but no lavage had to be abandoned because of ill effects. The median consumption of Klean-Prep was 1·4 (95 per cent c.i. 1·3–1·5) litres, compared with the 4 litres usually required for whole gut lavage in patients with an intact colon[8]. The lavage was complete in a median of 70 (95 per cent c.i. 60–80) min.

The WGLF IgG concentration was greater in patients with a high PDAI (*Table 1*) and positive Moskowitz criteria

Table 2 Comparison of whole gut lavage fluid parameters in patients with ('positive' Moskowitz criteria[14]) and without ('negative' criteria) pouchitis

	Moskowitz criteria		
WGLF parameter	Negative (n = 37)	Positive (n = 5)	P*
IgG (μg/ml)	3 (1–16)	31 (12–69)	< 0·001
Albumin (μg/ml)	8 (3–26)	45 (16–69)	0·001
α_1-Antitrypsin (μg/ml)	4 (1–44)	8 (5–32)	0·015

Values are median (range). IgG, immunoglobulin G; WGLF, whole gut lavage fluid. *Mann–Whitney U test

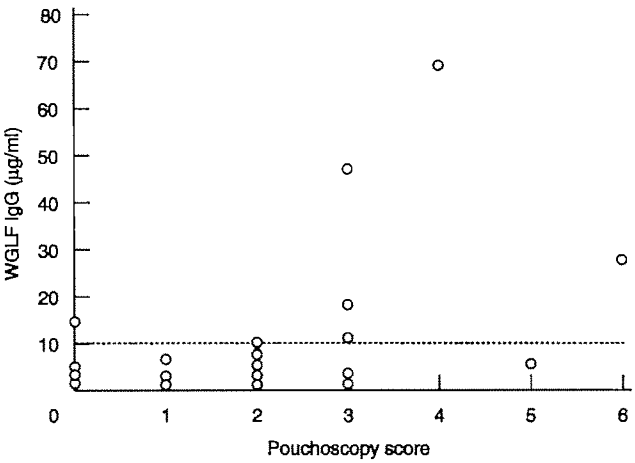

Fig. 1 Pouchoscopy score related to whole gut lavage fluid (WGLF) immunoglobulin (Ig) G concentration. The dotted line represents the upper limit of WGLF IgG concentration found in healthy volunteers and in patients with an immunologically normal intestine

(*Table 2*) than in those with a low PDAI or negative Moskowitz criteria. All five patients with pouchitis and positive Moskowitz criteria had a WGLF IgG level greater than 10 μg/ml. Three patients had a WGLF IgG concentration above 10 μg/ml but were negative according to Moskowitz criteria.

There was a significant correlation between the WGLF IgG concentration and PDAI ($n = 42$; $r_s = 0{\cdot}67$, $P < 0{\cdot}0001$). Two patients had a high PDAI (7 or more) but a low WGLF IgG level (less than 10 μg/ml). On the other hand, three patients had a low PDAI (less than 7) and a high WGLF IgG level (above 10 μg/ml). Nineteen patients had an essentially 'normal' pouch on pouchoscopy (score less than 1). All but one had a WGLF IgG level below 10 μg/ml. The WGLF IgG concentration related to the pouchoscopy score ($n = 42$; $r_s = 0{\cdot}05$, $P = 0{\cdot}0001$) (*Fig. 1*). The relationships of pouch biopsy neutrophil infiltration and chronic inflammation with WGLF IgG and albumin levels are shown in *Figs 2* and *3*.

WGLF albumin concentration correlated with WGLF IgG level ($r_s = 0{\cdot}79$, $P < 0{\cdot}0001$) and also with PDAI ($r_s = 0{\cdot}64$, $P < 0{\cdot}0001$). WGLF albumin concentration was highest in patients with severe neutrophil infiltration and with severe chronic inflammation (*Fig. 2* and *3*). Five patients had a WGLF albumin level greater than 26 μg/ml; all of whom had a WGLF IgG concentration greater than 10 μg/ml. Using a combination of WGLF IgG concentration above 10 μg/ml and WGLF albumin level greater than 26 μg/ml as diagnostic criteria for pouchitis, the present results gave one false-negative and one false-positive case of a total of 42, compared with the Moskowitz diagnostic criteria. Accordingly the sensitivity of the combined test was 0·80, whereas the specificity was 0·97. The receiver–operator characteristic curves for WGLF IgG and albumin levels are shown separately in *Fig. 4*.

Only two patients had a WGLF α_1-antitrypsin concentration greater than 19 μg/ml, a level that has been shown previously to indicate gut inflammation[10]. WGLF α_1-antitrypsin level did not correlate with the PDAI. The WGLF α_1-antitrypsin concentration, however, was significantly raised in patients with positive Moskowitz criteria ($P = 0{\cdot}015$) or with high PDAI ($P = 0{\cdot}002$).

Discussion

Pouchitis, a syndrome of diarrhoea, endoscopic stigmata of inflammation and features of biopsy neutrophilia and ulceration, has been hypothesized to be a form of IBD in ileoanal pouches[5]. The Mayo Clinic physicians therefore expanded the previously known Moskowitz criteria[14] to create a PDAI[13], similar to clinical disease activity indices used in IBD (e.g. the CDAI). Clinical disease activity indices have limitations based on their subjective bias; objective tests may be more useful in certain patients, such as adults with psychological disorders, children and adolescents[12].

This study shows that increased gut protein loss, as measured by WGLF IgG concentration, may also observed in patients with an ileoanal pouch. All patients with pouchitis, as defined by the Moskowitz criteria, had a WGLF IgG level of 10 μg/ml or above. WGLF IgG concentration also correlated with PDAI. This relationship of gut protein loss to endoscopic stigmata of inflammation and biopsy characteristics may indicate that protein-losing enteropathy is a true biological phenomenon observed in patients with an inflamed ileoanal pouch.

A similar correlation between protein-losing enteropathy, as measured by WGLF IgG concentration, and

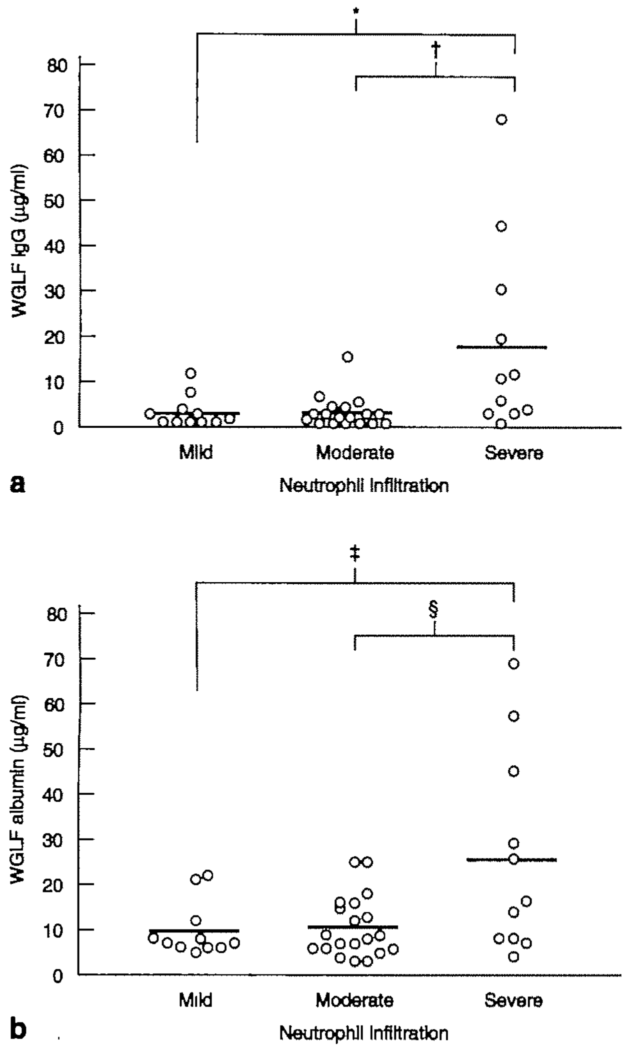

Fig. 2 Pouch biopsy neutrophil infiltration compared with

a Whole gut lavage fluid (WGLF) immunoglobulin (Ig) G and

b WGLF albumin levels. Horizontal lines represent the means of the samples. *$P = 0{\cdot}013$, †$P = 0{\cdot}062$, ‡$P = 0{\cdot}041$, §$P = 0{\cdot}043$ (χ^2 test)

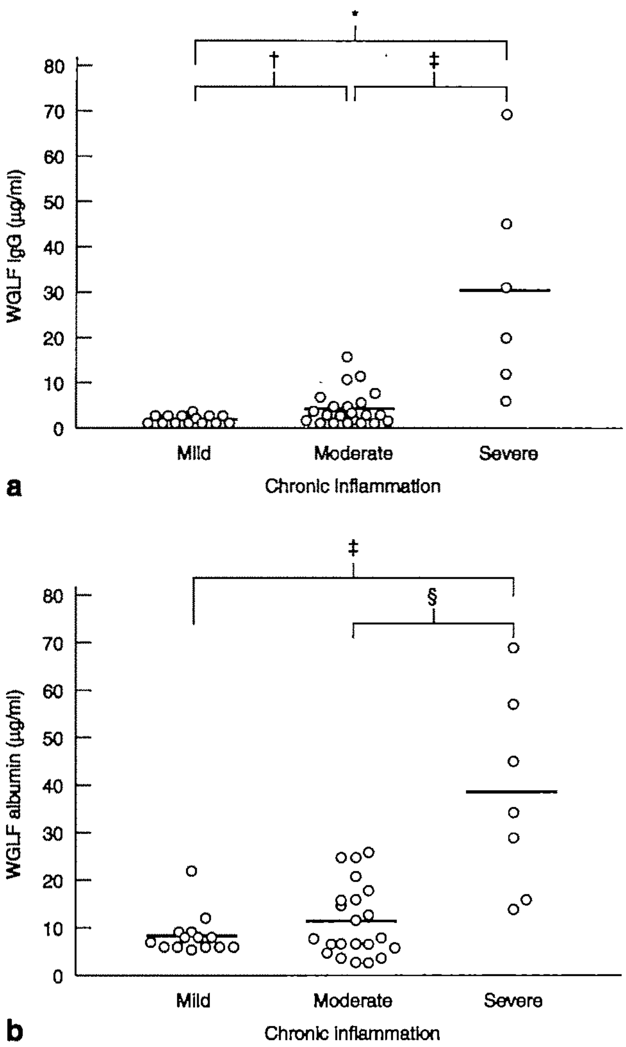

Fig. 3 Presence of chronic inflammation in pouch biopsies compared with

a Whole gut lavage fluid (WGLF) immunoglobulin (Ig) G and

b Albumin concentrations. Horizontal lines represent the means of the samples. *$P < 0{\cdot}001$, †$P = 0{\cdot}026$, ‡$P = 0{\cdot}001$, §$P = 0{\cdot}004$ (χ^2 test)

clinical disease activity has been observed in IBD[8]. The correlation, however, between PDAI and WGLF IgG concentration seems to be 'weaker' than that shown for IBD[8]. This may either be due to the definition of PDAI, or it may indicate that protein-losing enteropathy in patients with an inflamed pouch has different characteristics from that in other forms of IBD.

Patients who had a high PDAI and low WGLF IgG concentration (less than 10 µg/ml) were all negative for the Moskowitz criteria. This may signify the emphasis on the symptoms for the calculation of the PDAI. Patients who had a low PDAI but a high WGLF IgG concentration (greater than 10 µg/ml) had either florid anal columnar cuff inflammation or pouch dysfunction with relatively normal pouchoscopy findings. It is possible that the PDAI shares the limitations of other clinical disease activity indices (e.g. CDAI). In a study comparing CDAI, global clinical assessment and WGLF IgG concentration, CDAI was shown to be unreliable in psychologically disturbed patients and in children[12].

WGLF albumin concentrations correlated with the clinical disease activity index PDAI[8]. Although the plasma cell infiltrate in pouchitis is composed mainly of IgA- and IgG-bearing cells[17], the presence of albumin in the WGLF

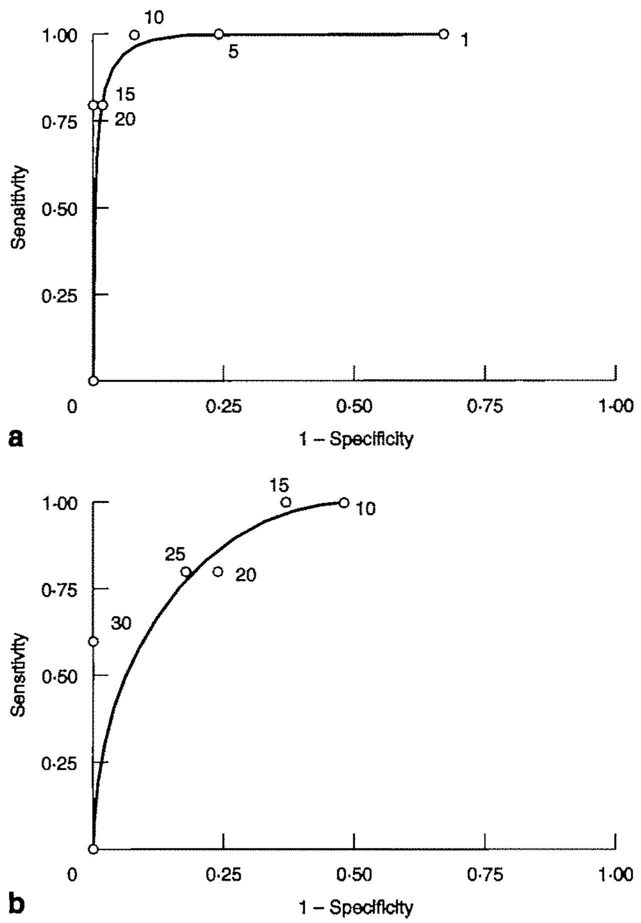

Fig. 4 Receiver–operator characteristic curve for

a Whole gut lavage fluid (WGLF) immunoglobulin (Ig) G and

b Albumin levels for diagnosis of pouchitis according to Moskowitz criteria. The numbers on the curve indicate WGLF IgG or albumin concentration

in parallel to the IgG may indicate that the protein loss is mainly plasma derived. Studies utilizing the new PDAI index are limited. Boerr *et al.*[18] measured faecal α_1-antitrypsin concentration by radial immunodiffusion in 33 patients with an ileoanal pouch and reported a correlation with PDAI. Such a correlation was not observed in the present study. This may be attributed to the different methodologies employed; immunoturbimetry was used in the present study. Faecal estimation of α_1-antitrypsin activity has been shown to be misleading[19] and therefore unreliable as a measurement of disease activity. The WGLF α_1-antitrypsin level, however, has been shown to characterize gut protein loss. In the present study patients with pouchitis and positive Moskowitz criteria had greater WGLF α_1-antitrypsin levels.

In conclusion, protein-losing enteropathy in ileoanal pouches has been observed in a similar fashion to that in IBD. This finding may have practical use in the objective estimation of disease activity in cases of pouch inflammation. WGLF proteins may play an important role in the further study of the pathophysiology of pouchitis. Estimation of WGLF IgG and albumin levels may form a useful tool in the assessment of pouchitis and its treatment. The latter may require the need for further prospective studies.

Acknowledgements

The authors acknowledge the expertise of Drs A. M. Lessels, M. A. McIntyre, J. Webb, J. Thomas and K. M. McLaren in providing histological information from the pouch biopsies. They dedicate this paper to the memory of late Professor Anne Ferguson, who initiated the project.

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On-line quantitative analysis of surface electromyography of the pelvic floor in patients with faecal incontinence

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Background: Needle electromyography (EMG) remains the 'gold standard' for the assessment of external anal sphincter innervation. It is, however, an invasive and poorly tolerated technique. In this study a quantitative form of surface electromyography was compared with needle EMG of the external anal sphincter.

Methods: Invasive needle EMG to assess mean fibre density and neuromuscular jitter was compared directly with quantitative surface EMG in 37 patients with faecal incontinence and 12 age-matched controls.

Results: There was a significant positive correlation between mean fibre density on needle EMG and maximum turns rate on surface EMG ($r_s = 0{\cdot}48$ (95 per cent confidence interval 0·28–0·76), $P = 0{\cdot}003$). Furthermore, surface EMG was able to discriminate between patients with normal neuromuscular jitter and those with increased jitter, a measure of progressive denervation and reinnervation, on the basis of reduced rectified mean surface signal ($P = 0{\cdot}02$, Fisher's exact test).

Conclusion: Quantitative surface EMG may potentially replace invasive needle EMG as the investigation of choice in the assessment of anal sphincter electrophysiology.

Presented in part to a meeting of the American Society of Colon and Rectal Surgeons, Montreal, Canada, May 7–12 1995

Paper accepted 9 December 1999

British Journal of Surgery 2000, 87, 814–818

Introduction

Needle electromyography (EMG) remains the 'gold standard' for assessment of neuropathic changes in the pelvic floor and anal sphincter muscles of patients with faecal incontinence. Important information regarding previous partial denervation and reinnervation may be obtained from the mean fibre density[1] and the stability of pelvic floor innervation at the time of investigation reflected by neuromuscular jitter[2]. EMG is, however, an invasive and uncomfortable procedure and has therefore fallen into relative disuse. This is particularly so because ultrasonography provides information not only about the structural integrity of the anal sphincter complex, but also, by interpretation of the thickness of the various muscle layers, about the neurological status of the striated muscles.

Discomfort is common to needle EMG, whatever the site, and many neurophysiologists have allied surface recordings to sophisticated signal analysis hardware and software in an attempt to improve patient acceptability[3–9]. Simple surface EMG has been widely tested in the assessment of patients with faecal incontinence[4,10] but has been limited by the subjective nature of interpretation of the surface signals recorded. In this study the newer sophisticated EMG techniques were adapted for use in patients with faecal incontinence.

Quantitative surface EMG analysis relies upon interpreting the signals recorded from the skin overlying a muscle. In the theoretical case of a spherical muscle composed of evenly distributed equally sized motor units all recruited at equal rates upon active voluntary contraction, the net potential recorded on the surface would be zero as all the action potentials would cancel. However, this is not the case in practice and the surface electromyogram is a complex sine wave composed of evenly spaced positive and negative potentials of approximately the same amplitude. If the motor units are of unequal size and unequally distributed throughout the muscle, the action potentials from one motor unit are not cancelled by those from other units and a net potential is recorded on the muscle surface[11].

Normal muscles are not spherical with equal distribution and recruitment of motor units, but the same principle holds true. Denervation and compensatory reinnervation of a muscle leads to the formation of large dominant motor units which, when activated, produce characteristic large-amplitude surface action potentials[6]. Each spike in the action potential represents the sum of the individual action potentials occurring synchronously at that time. The more large-amplitude spikes that are seen, the greater the number of large motor units with all fascicles discharging synchronously. This may be recorded as the turns rate[11], with a turn counted as each time the surface action potential vector changes direction by 90–180° irrespective of its absolute value relative to the reference electrode (i.e. the turns rate is a measure of the number of small spikes that, summated, form the surface potential).

During any given period of muscular contraction, if the mean numerical value of the voltage recorded at set intervals from the skin overlying the muscle is calculated, irrespective of its polarity in relation to the reference electrode, the result is the rectified mean surface signal strength. The rectified mean would be expected to increase as the normal distribution of evenly sized motor units in the muscle belly is replaced by an arrangement of asymmetrically placed larger motor units produced by denervation and reinnervation. Whereas, initially, the small evenly spaced motor units would cancel one another out in terms of surface action potential, larger asymmetrically placed motor units will produce recordable potentials at the skin overlying the muscle – as in the production of an electrical potential on the surface by myocardial activity. Mean fibre density[1] and turns rate[11] are both regarded as measures of compensatory reinnervation after disruption of the lower motor neurones supplying skeletal muscle. It has been suggested that the rectified mean signal recorded during voluntary contraction may fall in cases of acute nerve injury, whereas stable reinnervation after nerve injury may lead to an increase in rectified mean signal strength as dominant large motor units discharge synchronously.

This study attempted to determine whether these new analyses of surface electrical recording were comparable with traditional invasive needle EMG in a group of patients with faecal incontinence and age-matched control subjects.

Patients and methods

Recordings of surface and single-fibre EMG for both mean fibre density and jitter analysis were obtained from 37 patients with faecal incontinence and 12 age-matched controls. All patients and controls were women.

The hardware and incorporated software were developed 'in house' from commercially available units and used to investigate the changes in the innervation of muscles in chronic neurological conditions such as multiple sclerosis[12], partial denervation and muscle degeneration[13]. Surface recordings were made by attaching paediatric electrocardiographic electrodes (Biotrace-NS Bio-Adhesive Neonatal ECG electrodes; MSB, Ramsbury, Marlborough, UK) to the perianal skin, having first cleaned the area with an alcoholic wipe. The signal detected was amplified with an EMG amplifier (model AB601G; Nihon Kohden, Tokyo, Japan) and then processed by a four-board transputer allied to a 486 microcomputer running appropriate software. The data were stored on the computer's hard disk, and data files were transferred to Microsoft Excel (Microsoft, Reading, UK) for analysis. Of the various analyses available, turns rate and rectified mean were the two parameters used in this study.

To record mean fibre density a 13K87 single-fibre EMG needle (Dantec, Bristol, UK) was used in conjunction with a Neuromatic 2000 Electrophysiology Unit (Dantec). The subject and investigator were both earthed and the needle was passed through the perianal skin without anaesthetic into the external anal sphincter. When electrical activity was detected, the trigger level and slope controls of the electrophysiology unit were adjusted to isolate recordings from one motor unit only. The number of action potentials seen was recorded and the needle repositioned to make another recording. The mean number of action potentials recorded in 20 needle positions was taken as the mean fibre density, a value which has no units.

Neuromuscular jitter was determined simultaneously. A 13K87 single-fibre EMG needle was used in conjunction with a Neuromatic 2000 Electrophysiology Unit as described above. The jitter analysis was performed by software provided by Dantec, installed on a personal computer connected to the electrophysiology unit via an IEEE 48 board supplied and fitted by Dantec. After identifying and isolating a motor unit with two or more muscle fibres within the recording range of the single-fibre EMG needle, the mean difference in interval between two selected action potentials over 200 consecutive discharges of that motor unit was calculated automatically. This is termed the mean consecutive difference or 'jitter'. This was repeated in at least ten positions in the external anal sphincter, and the mean jitter was calculated. The authors have previously demonstrated that in normal controls neuromuscular jitter does not exceed 50 μs in the external anal sphincter[2].

Results

Turns rate recorded from the perianal skin overlying the external anal sphincter was correlated with mean fibre

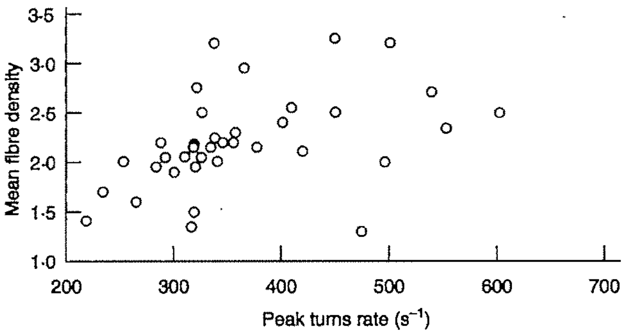

Fig. 1 Relationship between mean fibre density and turns rate for the external anal sphincter ($n = 37$)

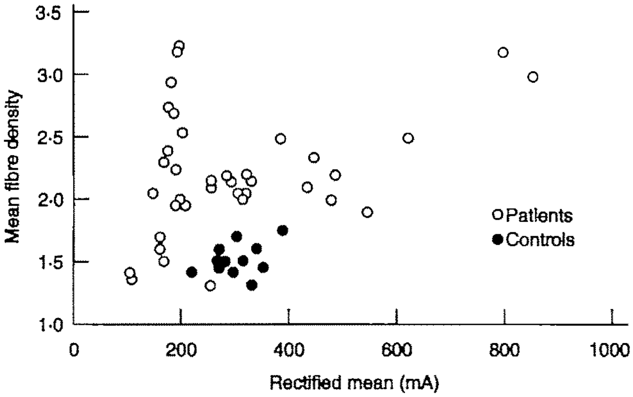

Fig. 2 Relationship between mean fibre density and rectified mean signal strength for subjects ($n = 37$) and controls ($n = 12$)

Table 1 Relationship between neuromuscular jitter and rectified mean surface signal strength

	Mean jitter (µs)	
	>50	<50
Rectified mean (mA)		
≥300	4	9
<300	17	7

$P = 0.02$ (Fisher's exact test)

density in the external anal sphincter. The results are illustrated in *Fig. 1*, which shows that there was a significant positive correlation between the two modalities ($r_s = 0.48$ (95 per cent confidence interval (c.i.) 0·28–0·76), $P = 0.003$).

Mean fibre density was plotted against rectified mean for the 37 patients in the study. The resulting data described a parabolic curve (*Fig. 2*). Twelve control subjects also underwent mean fibre density estimation and surface EMG. In controls the mean fibre density was 1·6 (95 per cent c.i. 1·4–1·75) and the rectified mean 304 (221–389) mA. They therefore occupied a position at the point of inflexion in *Fig. 2* (i.e. between two groups of incontinent patients). In one group of patients with faecal incontinence, an increase in mean fibre density was associated with an increase in rectified mean surface signal strength. In the other group an increase in mean fibre density was associated with a decrease in the rectified mean. The relationship between rectified mean and neuromuscular jitter for the patients studied is shown in *Table 1*.

Discussion

Invasive EMG is poorly tolerated and little used in the clinical assessment of incontinent patients. A major problem with surface EMG is that, although abnormal patterns of activity may be recognized subjectively, it has been difficult to measure objectively anything other than basic parameters such as duration of activity or maximum voltage recorded. A transputer-based system allows rapid data capture and on-line analysis to be performed[14]. Transputers are based on two or more processing units which acquire raw data in real time to the maximum of their capacity and then pass the task of data collection on to the next unit. While the next and subsequent units are collecting data, the first will analyse its pool of raw data and then store, analyse and present the results of the analysis to a computer screen in a real-time frame unit. This not only reduces the storage capacity required but also allows decisions to be made on the basis of the analysis while data are still being collected. This increases the speed and flexibility of the data handling system and was developed for use in situations where data have to be acquired, analysed and acted upon rapidly. The earliest transputers were developed for military uses such as missile tracking. Transputers have been allied to invasive needle EMG previously[15].

It is apparent from *Fig. 1* that there was a significant positive correlation between turns rate and mean fibre density in the patients studied. There was a broad spread of data, as indicated by the wide 95 per cent c.i. This may be due to a number of reasons. First, turns rate is a measure of muscular activity during a maximal squeeze effort, whereas mean fibre density is measured at rest. There is no evidence that the degree of activation alters functional motor unit size, but this could theoretically occur. Second, turns rate is a measure of the activity of the muscle as a whole, whereas mean fibre density looks in great detail at a relatively small number of motor units (typically 20). It is therefore possible that the turns rate, because of the larger sample size, is a more accurate reflection of the neurological status of the muscle than mean fibre density.

Fig. 2 indicates that patients with faecal incontinence fell into two broad groups. One group displayed an increase in rectified mean surface signal strength with increasing mean fibre density, and this was associated with normal neuromuscular jitter. This group represents subjects in whom stable reinnervation has occurred and large dominant motor units, firing synchronously, produced large surface action potentials. The other group displayed decreasing rectified mean surface signal strength with increasing mean fibre density, and this was associated with an increase in neuromuscular jitter. This indicates that in these patients the reinnervation did not result in large, synchronously discharging, motor units, although reinnervation had occurred. This would indicate a relative failure of satisfactory and stable reinnervation following neurotmesis. It therefore appears that, in patients with faecal incontinence, the presence of a rectified mean surface signal of less than 300 mA, as recorded by this equipment, is associated with impaired reinnervation following nerve injury, as demonstrated by an increase in neuromuscular jitter, whilst a rectified mean surface signal greater than 300 mA is associated with stable reinnervation and the presence of large synchronous motor units. As with assessment of turns rate and its correlation with mean fibre density, the correlation is not absolute and much work remains to be done.

EMG has fallen into relative disuse with the advent of endoanal ultrasonography and also because of the unpleasant nature of the investigation. Although ultrasonography has obviated the need for electomyographic mapping of the external anal sphincter to locate injuries, and may also give an estimate of the neurological integrity of the striated muscle by measuring its thickness, surface EMG may allow easy and accurate assessment of the neurological status of the pelvic floor muscles and, as such, may be more widely acceptable and useful in conjunction with sophisticated imaging techniques.

Development of specific endoanal probes and further advances in software technology, allied to histological examination of muscle biopsies in patients who have been investigated before operation, may lead to surface EMG and signal analysis becoming a powerful non-invasive means of investigation for patients with pelvic floor disorders. As it is, there is renewed interest in neurological dysfunction of the pelvic floor and anal sphincter complex, and considerable effort is being made to standardize invasive EMG techniques[16]. Such invasive techniques may possibly be supplanted by a quantitative surface EMG probe and this technique may enable pelvic floor neurological trauma to be detected immediately postpartum with minimal discomfort. Patients at risk of incontinence and other pelvic floor disorders later in life may then be offered treatment to attempt to offset such problems before they become clinically apparent.

Acknowledgements

A.S.G. was supported by the Wellcome Trust.

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Original article

Long-term results of arteriovenous fistulas using transposed autologous basilic vein

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Background: The transposed autologous basilic vein to brachial artery arteriovenous fistula provides vascular access in the absence of adequate superficial vein. The long-term patency and complication rates of this conduit are largely unreported.

Patients and methods: Seventy-four brachiobasilic fistulas were performed in 65 patients. This was a secondary or tertiary access procedure in 84 per cent of patients.

Results: Of the 74 fistulas performed, 50 were successfully used for dialysis (68 per cent) and 24 (32 per cent) were never used, including 13 fistulas that failed without being used for dialysis. Of the 74 fistulas, 46 per cent failed (*n* = 34), 10 patients died with a functioning fistula (*n* = 10) and five were transplanted. The 30-day secondary patency was 73 per cent at 1 year, 53 per cent at 2 years and 43 per cent at 3 years rate was 96 per cent. Cumulative secondary patency was 73 per cent at 1 year, 53 per cent at 2 years and 43 per cent at 3 years. Nineteen (26 per cent) fistulas underwent a further 19 operative procedures. Fifty-one (69 per cent) fistulas developed complications. The most common complications were arm oedema (24 per cent), thrombosis (22 per cent) and bleeding (18 per cent).

Conclusion: In high-risk patients the autologous transposed brachiobasilic fistula has equivalent patency and lower complication rates than those reported for polytetrafluoroethylene interposition grafts.

Paper accepted 27 December 1999

British Journal of Surgery 2000, 87, 819–823

Introduction

The radiocephalic arteriovenous fistula[1] remains the first choice vascular access procedure for patients requiring long-term haemodialysis. Their extended life expectancy, accompanied by improvements in haemodialysis, has led to an increasing number of patients requiring secondary or tertiary vascular access procedures. In the absence of suitable superficial veins in the arms owing to previous fistula formation or venepuncture, the choice of vascular access is generally between a transposed autologous vein and a prosthetic graft. More recently the results of polytetrafluoroethylene (PTFE) arteriovenous grafts have improved, with 1-year secondary patency rates ranging from 80 to 90 per cent[2,3]. Furthermore, they are always available, have a high technical success rate and may be cannulated much earlier than autologous vein[2,4]. PTFE grafts, however, are associated with a high complication rate (60–100 per cent), including infection and thrombosis, and require an average of one operation per graft per year to maintain patency[4,5]. The brachial artery to transposed (autologous) basilic vein arteriovenous fistula (BB AVF) has received less attention. Early reports of potency and complication are promising, with primary patency rates of 75–90 per cent at 1 year[3,6]. Few studies have assessed long-term patency. The aim of this study was to evaluate the long-term patency rate and complications associated with BB AVF for long-term haemodialysis.

Patients and methods

Over 5 years, 74 BB AVFs were performed in 65 patients: 29 men and 45 women of median age 61 (range 24–94) years. BB AVF was the procedure of choice in the absence of adequate superficial vein in the upper limbs, i.e. a radiocephalic or brachiocephalic fistula was not possible. PTFE grafts were performed in the absence of suitable basilic vein. Six hundred and twenty wrist fistulas, 208 brachiocephalic fistulas and 13 upper limb PTFE grafts were performed during the same time interval. The left arm was preferred in 50 patients. Furthermore, 19 patients underwent additional procedures including simultaneous Permacath insertion

($n = 11$), ligation of a pre-existing fistula ($n = 6$), Permacath removal ($n = 2$) or removal of a peritoneal dialysis tube ($n = 1$). This was the first vascular access procedure in 12 patients, the second in 27, the third in 27 and the fourth or fifth in eight. Thirty-eight patients (58 per cent) had previously undergone unsuccessful peritoneal dialysis.

Forty-two patients (57 per cent) previously had a temporary subclavian vein dialysis catheter on the side of the fistula, with a total of 104 ipsilateral subclavian catheters and a median of one per patient (range 0–9). Thirty-two patients had preoperative imaging of the central (subclavian and brachiocephalic) and arm veins. This identified 16 central venous stenoses, eight on the side of the intended fistula. Three of these patients underwent subclavian vein angioplasty with stent insertion prior to fistula formation. Data were collected retrospectively from patient case notes and no patients were lost to follow-up.

BB AVFs were fashioned using a technique similar to that described previously[7,8]. A single dose of co-amoxiclav 1·2 g was given preoperatively to every patient, heparin was not administered routinely. The fistula was allowed at least 6 weeks to develop before venepuncture for haemodialysis.

Definitions of patency and success

For the purposes of this study fistulas were classified as successful, never used for dialysis or failures. Technical success was defined as the presence of a thrill on palpation or a bruit on auscultation 24 h postoperatively. Cumulative secondary patency refers to the number of fistulas functioning, regardless of the number of interventions required to maintain patency, and excludes fistulas that were never used for haemodialysis for whatever cause. When no attempt had been made to needle a patent fistula it was designated as never used. Failure was defined as inability to use the fistula for haemodialysis due to a cause other than transplantation or death. Operative ligations were classified as failures. Patients who underwent renal transplantation were considered as lost to follow-up and not as technical failures. Deaths unrelated to fistula failure were also treated as lost to follow-up. Complication rates refer to fistula-related problems only and included the causes of fistula failure.

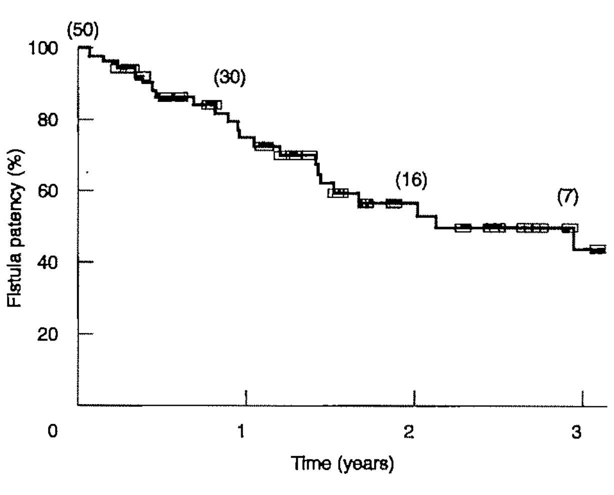

Fig. 1 Cumulative secondary patency of 50 brachiobasilic arteriovenous fistulas that were used successfully for dialysis

Statistical analysis

Kaplan–Meier life-table analysis was used to evaluate the cumulative overall and functional patency of the fistulas. No statistical analysis of risk factors for fistula loss or complications was performed owing to the small numbers involved.

Results

Of the 74 fistulas, 50 were successfully used for dialysis (68 per cent) and 24 were never used (32 per cent). In another 5 cases the procedure was abandoned because of an inadequate basilic vein found at operation, representing a 93 per cent technical success rate. The median duration to first use was 70 days ($n = 50$). Of the 24 fistulas never used, 11 (18 per cent) failed prior to use for haemodialysis due to failure to develop (5), ligation (3) [because of infection (2), or steal (1)], thromboses (2) or arm oedema secondary to superior vena cava obstruction (1). Of the remaining 13 fistulas 4 are currently maturing, 4 patients died, 1 patient received a renal transplant and two patients never used their fistula because of recovery of renal function ($n = 1$) or conversion to peritoneal dialysis ($n = 1$). Two fistulas remain patent in pre-dialysis patients.

Patency

Of the 74 fistulas, 34 failed (46 per cent), 10 patients died with a functioning fistula and five received a renal transplant. The 30-day secondary patency rate was 96 per cent (two ligated and one thrombosed). Median patency was 18·4 months. Of the 34 that failed, 11 were never provided adequate haemodialysis and cumulative secondary patency was 73, 53 and 43 per cent at 1, 2 and 3 years respectively (*Fig. 1*). The causes of fistula failure are summarized in *Table 1*. Of the seven fistulas that needed ligation, three were ligated for septic complications, including two with a ruptured mycotic aneurysm and one with a false aneurysm; two other patients had severe arm oedema and two had steal.

Morbidity and mortality

Median hospital stay was 5 days (range 2–165). Thirty-three patients required a total of 52 readmissions with complications related to the fistula (total additional hospital stay of 265 days, mean 4 days per patient). Nineteen patients underwent a further 19 operative procedures on their brachiobasilic fistula including re-exploration ($n = 3$), operative ligation ($n = 7$) or revision ($n = 9$). Indications for further operative procedure are summarized in *Table 2*. In addition, 3 patients required stenting of a previously undiagnosed central vein stenosis.

Fifty-one (69 per cent) developed complications (*Table 3*). There were no deaths directly attributable to surgery, however, two patients died of unrelated causes within 30 days of surgery.

Arm oedema was the most common complication and occurred in 18 (24 per cent) cases. Of these, 11 (61 per cent) developed arm oedema within 30 days after surgery. Most were managed conservatively ($n = 10$) but one patient required fistula ligation. The causes of late arm oedema were identified in four patients and included thrombosis of a subclavian vein stent (one), treated with thrombolysis, basilic vein stenosis (one), leading to poor flow and eventual thrombosis, and subclavian vein stenosis (two) treated with subclavian vein angioplasty and stent insertion. One further fistula required ligation for severe arm oedema and ischaemia, and two were managed conservatively. Of four patients with documented venous hypertension defined as raised venous dialysis pressure, three failed secondary to poor flow and one was treated successfully with a subclavian vein stent.

Of the eight patients with radiological evidence of an ipsilateral central venous stenosis before formation, two fistulas never developed, four developed venous hypertension with poor flow, one patient developed bleeding from a needle site with eventual thrombosis and one patient died before fistula maturation at 6 weeks.

Thrombosis occurred in 16 fistulas (22 per cent) causing either early fistula failure ($n = 2$) or late fistula failure ($n = 10$). One patient underwent successful revision and three were managed successfully by resting the fistula for 6 weeks. Seven additional fistulas (9 per cent) developed flows too poor to achieve adequate dialysis and were considered to have failed.

Bleeding occurred in 13 fistulas (18 per cent), five in the early postoperative period and eight at least 30 days after surgery. Early bleeding was managed in three cases by immediate re-exploration and in two cases by simple pressure. Late bleeding from needle puncture sites was associated with high venous pressure. One patient developed a false aneurysm that needed ligation, and two developed haematomas, leading to thrombosis in one and infection with mycotic aneurysm formation and bleeding in the other.

Table 1 Causes of brachiobasilic fistula failure

Cause of failure	*n*
Thrombosis	12 (35)
Poor flow	7 (21)
Ligated	7 (21)
Never developed	5 (15)
Venous hypertension	1 (3)
Arm oedema	2 (6)
Total (percentages in parentheses)	34

Table 2 Indications for reoperation

	Re-exploration	Revision	Ligation
Bleeding	3		
Infection			3
Steal		1	2
Aneurysm		1	
Arm oedema			2
Venous hypertension			
Poor flow		3	
Slow to develop		2	
Thrombosis		2	
Total	3	9	7

Table 3 Complications

	Early	Late	Total
Arm oedema	11	7	18 (24)
Thrombosis	2	14	16 (22)
Bleeding	5	8	13 (18)
Infection	6	5	11 (15)
Steal	7	4	11 (15)
Slow to develop		11	11 (15)
Poor flow	0	7	7 (9)
Venous hypertension	1	3	4 (5)
Aneurysm	0	3	3 (3)
Lymph leak	2	0	2 (3)
Cardiac failure	0	1	1 (1)

Values in parentheses are percentages

Infection of the wound occurred within 30 days of fistula formation in six (8 per cent) cases, two following early fistula revision. This was treated by antibiotic therapy ($n = 5$) or ligation because of a collection adjacent to the vascular anastomoses ($n = 1$). Late infection was associated with needling sites and led to thrombosis in one patient and mycotic aneurysm formation and bleeding in another.

Arterial steal, defined as distal ischaemia presenting as claudication, paraesthesia, muscle wasting or tissue loss, occurred in 11 cases (15 per cent). Two fistulas required ligation, one was revised and eight were managed conservatively. One patient (1 per cent) developed high-output cardiac failure that resolved following spontaneous fistula thrombosis.

Discussion

The BB AVF was first described in 1966[1] but few previous reports document long-term patency rates. This study demonstrates that the BB AVF is a reliable form of vascular access for long-term haemodialysis in the absence of suitable superficial veins at the wrist or elbow. The basilic vein is usually of greater diameter than the cephalic vein and it is rarely damaged by previous venepuncture because of its deep location. The primary success rate of 94 per cent is similar to those reported by others, which range from 88 to 95 per cent[3,6,9]. The cumulative secondary patency rate for BB AVF in this study was 73, 53 and 43 per cent at 1, 2 and 3 years respectively, and is comparable to that reported in other series[3,9–11].

The high percentage of fistulas never used for dialysis in the present series, as well as the overall complication rate of 69 per cent, is probably due to the number of high-risk patients included in the study. For example the number of primary procedures is much lower than that reported in other series[6,9,10,12], including 35 patients with at least two previous failed vascular access procedures as well as 38 who had previously been unsuccessful with peritoneal dialysis. In addition, the number of previous subclavian temporary dialysis catheters inserted before fistula formation was high. This, taken together with the 11 per cent rate of subclavian stenosis diagnosed before surgery, is a significant risk factor for the high incidence of arm oedema (24 per cent)[13–16]. In an effort to reduce the scale of this problem it is suggested that the exclusion of central vein stenoses by a combination of clinical examination and preoperative venography is important in patients with previous subclavian catheterization. Patients with postoperative arm oedema should be investigated with venography or colour duplex imaging with a view to venous angioplasty[15,16] as an alternative to fistula ligation, should conservative measures such as arm elevation fail. In this study five patients had a subclavian vein stenosis identified prior to surgery that appeared to be radiologically insignificant. Formation of a BB AVF was still thought to offer the best chance of long-term vascular access in these patients.

These results compare favourably to similar studies using PTFE interposition grafts, with reported secondary patency rates between 40 and 50 per cent at 3 years, and complication rates of 60–100 per cent[2,5,17]. In particular, the reoperation rate after PTFE grafts is much higher, ranging from 45 to 67 per cent[5,18] one revision every 1·4 years[4]. Use of transposed autologous basilic vein has several other advantages over PTFE. First, only one anastomosis is required; and the distal venous anastomosis, the most common site of stenosis in PTFE grafts, is therefore avoided. Second, the development of local infection does not mandate removal of an autologous vein fistula; of 11 infections reported in this study, eight were successfully treated conservatively. Two complications that have been mentioned as a possible disadvantage of brachiobasilic fistulas are high-output cardiac failure and arterial steal, both caused by the high flow rates associated with brachial artery fistulas. The 1 per cent incidence of cardiac failure in the present study was lower than that reported by others[19], whilst the incidence of steal was high in this series, intervention was required in only three patients.

In summary, for patients with inadequate superficial veins in the upper limb the transposed brachiobasilic fistula has long-term results comparable to those using a PTFE interposition graft. Patients who are considered for brachiobasilic fistula formation who have had previous ipsilateral subclavian dialysis catheters may benefit from radiological imaging of their central veins prior to surgery in order to exclude a stenosis that may culminate in reduced patency.

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Value of herniography in the management of occult hernia and chronic groin pain in adults

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Introduction

Groin pain is a frequent presenting complaint to surgeons and has many causes. Inguinal hernias are a common cause and normally present as a reducible mass with a cough impulse. However, pain may be the only clinical feature. Herniography is a useful diagnostic tool in the investigation of obscure groin pain where the diagnosis of hernia cannot be excluded by examination. This paper reports a series of 80 patients with occult groin pathology who underwent herniography.

Patients, methods and results

Eighty patients underwent outpatient herniography carried out by the same consultant radiologist between 1996 and 1998 using a technique described by Ekberg[1]. Sixty-four men and 16 women aged 24–86 (mean 48, median 55) years were studied. Indications for herniography were pain in 68 patients (85 per cent), mass in seven (9 per cent) and possible recurrent hernia in five (6 per cent). *Table 1* shows the herniography findings. Nineteen patients (24 per cent) were found to have one or more hernias (*Fig. 1*). Of these, 13 patients presented with pain, three complained of a mass and three defined a clinically occult recurrent hernia. There were six unexpected findings at herniography: four bilateral and two dual (ipsilateral direct and indirect) hernias. Patients with a negative herniographic finding underwent further investigation (computed tomography, ultrasonography, contrast studies or laparoscopy as indicated) and were followed as outpatients until an alternative diagnosis was made or symptoms abated. In 84 per cent (51 of 61 patients) the symptoms resolved spontaneously. Mean time for resolution was 20 (range 6–52) weeks. In the remaining ten patients other diagnoses were made: diverticular disease, irritable bowel syndrome, osteoarthritis, ovarian cysts and chronic prostatitis.

Fifteen patients with a positive herniographic finding underwent operation. Surgical findings correlated exactly with those predicted by herniography in 11 patients. Inconsistencies included two patients with predicted bilateral hernias with only one (on the symptomatic side) found at operation, a patient with dual hernias when a direct hernia only was predicted, and one false-positive herniogram. There were no known false negatives, giving 100 per

Table 1 Results of herniography in 80 patients

	Frequency
No abnormality	61 (76)
Unilateral direct hernia	8 (10)
Bilateral direct hernia	2 (2)
Unilateral indirect hernia	4 (5)
Bilateral indirect hernia	2 (2)
Dual hernias	2 (2)
Femoral hernia	1 (1)

Values in parentheses are percentages

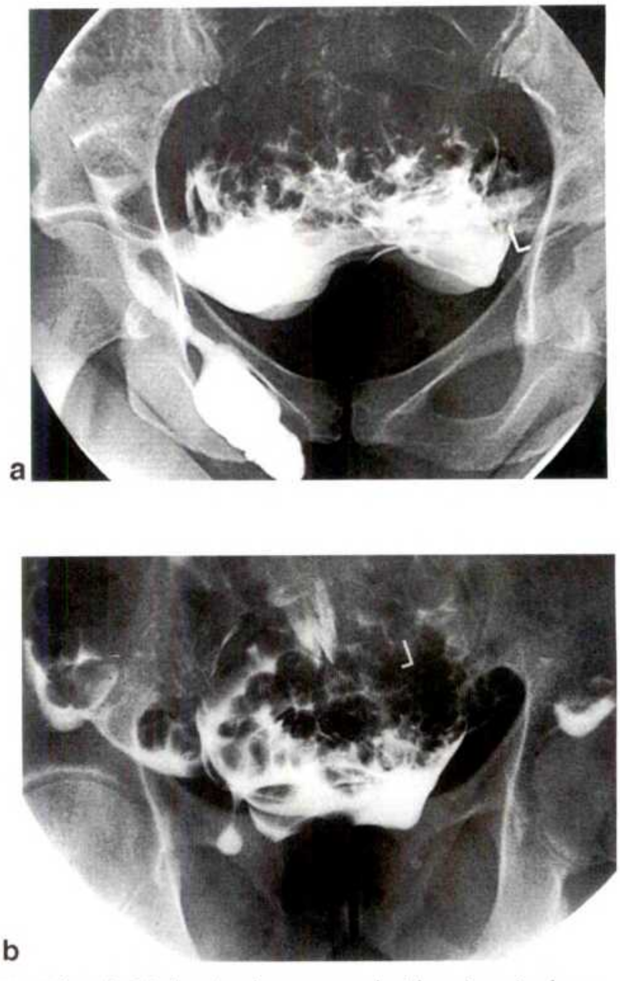

Fig. 1 Impalpable hernias that presented with groin pain alone:
a Right indirect hernia
b Right femoral hernia

cent sensitivity, 98 per cent specificity and a positive predictive value of 93 per cent for herniography in diagnosing an occult groin hernia.

Three of the 80 patients experienced complications with the introduction of the contrast medium (two patients had vasovagal bradyarrhythmias and one had abdominal pain), but all recovered without sequelae.

Discussion

Herniography was first described in 1967[2], but the technique has not been widely reported in Europe. Its principal role is to establish the diagnosis of an occult hernia as a cause of obscure pain in the groin[3]. Groin pain with an unremarkable examination is the commonest clinical scenario leading to herniography. Most of these patients (76 per cent in the present study) have no herniographic abnormality and at follow-up the majority (84 per cent in this study) had self-limiting groin pain. Judicious investigation will thereby avoid unnecessary surgery in this common group of patients. With a mean time to resolution of 20 weeks and a significant complication rate from herniography[4], the authors suggest that an initial period of observation of 4 months (in the absence of clinical deterioration) is worthwhile before proceeding to herniography. Alternative techniques for evaluating abdominal wall hernias, including ultrasonography, computed tomography and magnetic resonance imaging[5], may have a role in the future.

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Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double spacing

Some personal thoughts on plagiarism

Sir

I was intrigued by a recent announcement concerning a peculiar incidence of plagiarism: a reviewer incidentally spotted an article from a non-English-speaking surgeon, in which an appreciable part of the introduction had been copied verbatim from a paper published by the reviewer a decade ago (*Br J Surg* 1999; **86**: 598–9). None the less, the author used his local data for statistical analysis. The 'misdemeanour' was dutifully denounced, rather relentlessly.

Immediately it came to me that if I were the reviewer, I would get pretty excited at finding the validity of my original claim reaffirmed by a further study encompassing a larger number of patients from a different population. I would hasten to help rephrase the duplicated sentences, hoping that the publication of their set of data would prove the reproducibility and, possibly, integrity of mine. It might be argued that I have put too much weight on data value. Anyway, it takes much more time and effort to produce the statistics than literacy presentation. Besides, the sentence structure can be changed while the data cannot.

Let us turn to the reverse (but more controversial) scenario, namely the same set of materials in a different guise. Some 4 years ago, the reputedly first case of endoscopic parathyroidectomy was described in a letter to the Journal[1]. Subsequently, full case reports of this patient appeared in two other journals, one for anaesthetists and the other for endoscopic surgeons[2–3]. Notably, there were discrepancies between the two case reports in some important data presented (*Table 1*), possibly resulting from attempts by different authors to support their own contentions in the interest of their respective specialty. Are all the above occurrences justified by the value of the clinical findings? Some more thoughts are awaited.

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Table 1 Comparison of clinical data presented in the two reports on the same case of endoscopic parathyroidectomy.

Case report by endoscopic surgeons[2]	Case report by anaesthetists[3]
'...carbon dioxide was then insufflated to 15 mmHg'	by insufflating CO_2 at an insufflation pressure of 20 mmHg'
'The patient developed mild hypercarbia (PaCO_2 between 41 and 45 mmHg) which was controlled by a slight increase in minute ventilation'	PaCO_2 of 63 mmHg...We increased the minute ventilation to more than 20L/min... However, the HR and the hypercarbia remained unchanged'
'The procedure took nearly 5h' '...no pain nor other complications related to the diffuse carbon dioxide'	'7-h surgery''Postoperatively, he had severe scrotal pain (emphysema) for the next 18 h'

Prospective study of safety, patient satisfaction and leg ulcer healing following saphenous and subfascial endoscopic perforator surgery

Sir

The article by Nelzén (*Br J Surg* 2000; **87**: 86–91) presents a series of 138 patients (146 operated legs) who underwent subfascial endoscopic perforator surgery (SEPS). In 89 per cent, saphenous vein surgery was also performed. However, the results in *Table 3* (postoperative morbidity, complications and complaints), *Table 4* (patient opinion regarding the cosmetic results), *Fig. 1* (patient opinion regarding symptomatic relief) and *Fig. 2* (cumulative leg ulcer healing) are presented as a consequence of the SEPS only. This is misleading as the results imply the effect of both the elimination of saphenous reflux as well as SEPS. Eleven legs demonstrated significant deep venous insufficiency, while all other legs had predominantly superficial venous insufficiency and/or perforator venous insufficiency. In primary varicose veins, the venous disturbance is due to saphenous reflux and not to incompetent calf perforators. This fact has been proved by means of strain gauge plethysmography[1]. Others[2–5] have shown that ligation of calf perforators does not improve the existing venous disturbance. Although many authors believe that incompetent calf perforators play a role in chronic venous insufficiency and especially in leg ulcers, nobody has so far proved that this presumption is substantiated. In Nelzen's series 17 patients had SEPS as a sole procedure, 11 of them had healed or open leg ulcers before operation. Unfortunately, the results in this small group with selective SEPS is not presented in detail. It is mentioned briefly in the discussion that all leg ulcers healed. No attempt was made to document plethysmographically or phlebodynamometrically the effect of selective interruption of incompetent calf perforators. As SEPS makes it possible to interrupt calf perforators without interference with saphenous reflux, it would be useful to perform a prospective study comparing selective SEPS with conservative therapy checking results by means of plethysmography or phlebodynamometry. The author of such a study might find that selective interruption of insufficient calf perforators does not improve venous haemodynamics and would conclude, like Linton, that 'this procedure plus a good stocking was as good as the stocking alone'.

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Author's reply

I agree that some of the legends could be misinterpreted outside the context of the article. There is always a balance between the amount of information that ought to be given and available space. The legends would have been more informative if 'with or without saphenous surgery' had been added.

It was beyond the scope of the article to assess the role of incompetent perforators and indications for SEPS, but I do not agree that it is scientifically proven that incompetent perforators do not play a role in chronic venous insufficiency. The fact that plethysmographic methods have been unable to detect any haemodynamic improvement, following selective perforating vein ligation, does not necessarily mean that incompetent perforating veins are harmless. It could simply mean that plethysmographic methods are not sensitive enough to detect these changes. A recent publication[1] suggested that 'photoplethysmography is a poor method of assessment of venous reflux after SEPS'. Furthermore, Proebstle *et al.*[2] demonstrated haemodynamic improvement and objective healing of leg ulcers following isolated SEPS in patients who had previously undergone saphenous surgery.

A randomized multicentre study is currently underway in Sweden (the SWESEPS study) to assess the role of incompetent perforating veins in patients with leg ulcers and combined saphenous incompetence. Meantime, I regard SEPS as a complementary procedure to regular superficial venous surgery and believe that SEPS, in combination with saphenous surgery *without* a stocking, is better than the stocking alone.

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Outcome measures after lower extremity bypass surgery: there is more than just patency

Sir

I read with interest the paper by Dawson and van Bockel (*Br J Surg* 1999; **86**: 1105–6). Arguments in support of an aggressive limb-salvage policy in limb-threatening ischaemia have been made in recent years, but successful limb salvage is not always associated with good function and return to normal living. This observation has promoted interest in the assessment of quality of life in patients with critical ischaemia. The ultimate therapeutic aim must be the efficient return of the individual to their premorbid lifestyle and in some patients this may be better achieved by amputation and rapid prosthetic rehabilitation. I wonder whether it would be better to try to identify the profile of patients in whom primary amputation should be the first choice. This would avoid unnecessary procedures, poor results and impairment of quality of life. Nevertheless, I agree that decision making in modern surgical practice is becoming increasingly complex and reports must involve issues such as clinical need, cost benefit and comparative value to both the individual and society.

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Authors' reply

Sir

We appreciate the interest in our article by Dr Caeiro. The aim of our study was to provide outcome measures allowing a comprehensive view of the effectiveness of lower extremity bypass surgery. We advocate additional clinical and quality-of-life data as outcome measures besides patency, limb salvage and patient survival. Armed with such information, patients can be given a more accurate picture of what to expect following surgery.

Some patients are more likely to benefit from an aggressive limb salvage policy and Caeiro comments that it would be better to identify patients in whom early amputation and rehabilitation would be best. This point of view is in agreement with ours and quality of life must be measured in vascular practice and research. Patient selection for bypass grafting or primary amputation continues to represent a major challenge in vascular surgery. Much research regarding this topic has been done[1–3], but objective criteria for patient selection are still lacking. This has resulted in conflicting conclusions in different studies[3].

We strongly believe that the benefits of bypass grafting or amputation in given clinical situations can be determined only after a more systematic and comprehensive application of outcomes research.

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1 Szilagyi DE, Hageman JH, Smith RF, Elliott JP, Brown F, Dietz Pl. Autogenous vein grafting in femoropopliteal atherosclerosis: the limits of its effectiveness. *Surgery* 1979; **86:** 836–51.
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Book reviews

Recent Advances in Coloproctology

J. Beynon and N. D. Carr (eds)

240 × 156 mm. Pp. 182. Illustrated. 2000. London: Springer Verlag. £80.

As the editors state in their preface, coloproctology is now a major sub speciality. This series of 10 articles written by experts in the field covers areas of major concern in an authoritative and well-written way, supported by good references. Ideally, there should be more illustrations, and some of the present ones could be made easier to follow with better labelling and fuller captions, however, the three dimensional representation of the anal canal on page 96 gives an exciting glimpse of the future. The illustration of the Lloyd-Davies position on page 56 is rather antique, with apparently tight bandaging of the legs on the stirrups (increasing the risk of thrombophlebitis, compartment syndrome and, perhaps, lateral popliteal nerve compression and the urinary catheter draining into a bottle! Perhaps the editors might have cross-referenced this with the wisdom of the chapter concerning the law. This notwithstanding, these 10 review articles are useful and this book, which appears to be the first of a series, is to be recommended.

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Acute pancreatitis. Novel Concepts in Biology and Therapy

W. Büchler, W. Uhl, H. Friess and P. Malfertheiner (eds)

239 x 168 mm. Pp. 497. Illustrated. 1999. Oxford: Blackwell Science. £69.50.

This book covers all aspects of acute pancreatitis from the physiopathology of the disease to the principles of treatment. Experts from around the world have participated in the making of this publication. The volume is divided in eight parts. The first two parts concern the events initiating pancreatitis. Although they report essentially experimental studies, these chapters are far from being boring and are always orientated toward clinical matters. The other parts cover the diagnosis and classification of acute pancreatitis, the role of infection, and medical and surgical treatments. The general purpose of the book is to answer practical questions in the light of up-to-date knowledge. The chapters are short, precise, and give clear conclusions. This book summarizes all the present knowledge about acute pancreatitis and discusses the new therapeutic drugs which are in development. It is a very useful tool for surgeons interested in this disease.

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Rob & Smith's Operative Surgery – Concise Vascular Surgery

C. W. Jamieson and J. ST Yao (eds)

282 x 224 mm. Pp. 339. Illustrated. 1997. London: Chapman & Hall Medical.

This is the fifth edition of Rob & Smith's Operative Surgery: Vascular Surgery. Intentionally, the more specialized operations have been excluded. The chapter on angiography is useful and well illustrated. Since the text is not specifically placed under each illustration, it is sometimes difficult to find the various anatomical details referred to on angiograms and ultrasound images. Similar objections are relevant for the chapter on intraoperative use of ultrasound, whereas the description of intraoperative angiography is clear and concise. Although, there may be personal preferences in the technique for exposing some of the major blood vessels, this chapter is informative with good black and white drawings.

In the reviewer's mind, the chapters on carotid endarterectomy, abdominal aortic aneurysm resection and operations for varicose veins are of outstanding quality. The chapters on infrainguinal reconstruction are also good, giving a useful step by step description of the operations. The chapter on management of arterial injuries is focusing on a few characteristic types of injuries, which are used as illustrations. It is doubtful whether the method of transatrial intracaval shunt deserves a whole page. For the treatment of late complications, the reviewer would have preferred that endovascular techniques had been included. The description of chemical sympathectomy is good, but the evaluation of the results in patients with atherosclerosis is too optimistic. Since this procedure has largely been abandoned, it would have been better to include chapters on thrombolytic therapy and some of the most common, well established endovascular techniques. Perhaps they could be included in the next edition of this book.

The black and white drawings are in general, of excellent quality and it is very valuable that each step of the operations as well as pitfalls and dangers are described. The paper quality and the format of the book is good. Some of the reference lists seem to be somewhat arbitrary. In conclusion, this book can be recommended as an introduction to operative vascular surgery for those specializing in general surgery, gastroenterologic-and orthopaedic surgery. It is also a good introduction book for vascular surgeons and interventional radiologists during their early period of training.

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Scientific Surgery

Belcaro G, Nicolaides AN, Errichi BM, Cesarone MR, DeSanctis MT, Incandela L *et al.* Superficial thrombophlebitis of the legs: a randomized, controlled follow-up study. *Angiology* 1999; **50:** 523–9.

Some 562 patients were all given compression and randomized into six groups receiving various combinations of surgery or anticoagulation; 3·5% had an established deep vein thrombosis. Progression of phlebitis was least after surgical stripping.

Junquera F, Lopez-Talavera JC, Mearin F, Saperas E, Videla S, Armengol J-R *et al.* Somatostatin plus isosorbide *5-mononitrate vs.* somatostatin in the control of acute gastro-oesophageal variceal bleeding: a double-blind, randomized, placebo-controlled clinical trial. *Gut* 1999; **46:** 127–32.

The addition of isosorbide adversely affected the control of bleeding (60 *versus* 87 per cent, $P = 0{\cdot}05$) and increased the development of ascites in this study of 60 patients. Transfusion and mortality rates were similar.

Peters FTM, Ganesh S, Kuipers EJ, Sluiter WJ, Klinkenberg-Knol EC, Lamers CBHW *et al.* Endoscopic regression of Barrett's oesophagus during omeprazole treatment: a randomised double blind study. *Gut* 1999; **46:** 489–94.

Sixty-eight patients were randomly allocated omeprazole or ranitidine. Ranitidine had no effect but omeprazole caused significant regression of Barrett's at endoscopy after 24 months.

Cao P, Giordano G, De Rango P, Zannetti S, Chiesa R, Coppi G *et al.* Eversion vs. conventional carotid endarterectomy: late results of a prospective multicentre randomized trial. *J Vasc Surg* 2000; **31:** 19–30.

Some 1353 patients were studied; mean follow-up was 33 months. The restenosis rate was less after eversion endarterectomy (3·6 *versus* 9·2 per cent, $P = 0{\cdot}01$), but was least after standard endarterectomy with patch closure (1·5%). Stroke and death rates were similar — 3·9 and 13·1% for eversion *versus* 2·2 and 12·7% for standard endarterectomy.

Kemeny N, Huang Y, Cohen AM, Shi W, Conti JA, Brennan MF *et al.* Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999; **341:** 2039–48.

The study involved 156 patients. All had systemic chemotherapy, half were randomly allocated hepatic arterial infusion. After 2 years, survival was improved in the patients who received combined treatment (86 *versus* 72 per cent, $P = 0{\cdot}03$)

Klinkenbijl JH, Jeekel J, Sahmoud T, van Pel R, Couvreur ML, Arnaud JP *et al.* Adjuvant radiotherapy and 5 fluorouracil after curative resection of carcinoma of the pancreas and periampullary region: phase III trial from the EORTC gastrointestinal tract cancer co-operative group. *Ann Surg* 1999; **230:** 776–82.

Chemoradiotherapy produced a small improvement in median survival in the 218 patients studied (24·5 *versus* 19 months).

deWit LT, Mathus-Vliegen L, Hey C, Rademaker B, Gouma D, Obertop H. Open vs. laparoscopic adjustable silicone gastric banding; a prospective randomized trial for treatment of morbid obesity. *Ann Surg* 1999; **230:** 800–5.

In this trial including 50 patients, both procedures were equally effective in first year weight loss. The laparoscopic procedure took longer (150 vs. 76 min) but required a shorter Hospital stay (5·9 *versus* 7·2 days) and fewer readmissions in the subsequent 12 months.

Chang L, Lo S, Stabile BE, Lewis RJ, Toosie K, de Virgilio C. Preoperative vs. postoperative endoscopic retrograde cholangiopancreatography in mild to moderate gallstone pancreatitis: a prospective randomized trial. *Ann Surg* 2000; **231:** 82–7.

Sixty patients at high risk of bile duct stones were included. Selective postoperative ERCP, done if bile duct stones were detected at operation, was necessary in 24% patients. This method reduced overall Hospital stay (9 *versus* 11.7 days) and was cheaper.

Tocchi A, Lepre L, Costa G, Liotta G, Mazzoni G, Maggiolini F. The need for antibiotic prophylaxis in elective laparoscopic cholecystectomy: a prospective randomized study. *Arch Surg* 2000; **135:** 67–9.

Some 84 patients were randomized to a single perioperative dose of 2g cefotaxime, or placebo. Infection rates were similar in each group (five *versus* seven, respectively).

Green RM, Abbott WM, Matsumoto T, Wheeler JR, Miller N, Veith FJ *et al.* Prosthetic above knee femoropopliteal bypass grafting: five year results of a randomized trial. *J Vasc Surg* 2000; **31:** 417–25.

This trial including 240 patients showed no difference in secondary patency for two different prosthetic grafts (dacron or polytetrafluoroethylene): both 68%. The risk of graft occlusion was increased in patients under 65 years and grafts < 7 mm diameter.

Ng EK, Lam YH, Sung JJ, Yung MY, To KF, Chan AC *et al.* Eradication of Helicobacter pylori prevents recurrence of ulcer after simple closure of duodenal ulcer perforation: a randomized controlled trial. *Ann Surg* 2000; **231:** 153–8.

Ninety-nine patients positive for H. pylori were randomized to eradication therapy or omeprazole only. One month ulcer healing rates were similar (82 *versus* 87%). Relapse rate after 1 year was significantly higher after omeprazole-only treatment (38 *versus* 5%).

Vermeulen EGJ, Stehouwer CDA, Twisk JWR, van den Berg M, de Jong SC, Mackaay AJC *et al.* Effect of homocysteine-lowering treatment with folic acid plus vitamin B6 on progression of subclinical atherosclerosis: a randomised, placebo-controlled trial. *Lancet* 2000; **355:** *517–22.*

Some 158 siblings of patients with premature atherosclerotic disease were studied for 2 years. Treatment reduced homocysteine levels and was associated with a reduction in the number of abnormal exercise ECGs.

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An article is reviewed for publication assuming that its contents have not been submitted simultaneously to another journal, have not been accepted for publication elsewhere and have not already been published. **Any attempt at dual publication will lead to automatic rejection and may prejudice acceptance of future submissions.** Please submit with your manuscript copies of any other papers (published, in press, or submitted for consideration elsewhere) that relate to the same subject. It is essential that you submit any other publications or submissions that use the same data set to allow assessment of any potential overlap. Indicate on the title page whether the paper is based on a previous communication to a society or meeting. Articles and their illustrations become the property of the Journal unless rights are reserved before publication.

Send four copies of original articles and other editorial matter to: The Editor, The *British Journal of Surgery*, Blackwell Science Ltd, 25 John Street, London WC1N 2BL, UK. Telephone: 0171 404 1831; facsimile: 0171 404 1927. Books for review should be sent to the same address.

A covering letter must accompany all submissions, must be signed by all authors and must state whether an abstract of the work has been published - please provide an appropriate reference. Disclose in the covering letter any potential or actual personal, political or financial interest you may have in the material, information or techniques described in the paper. The Journal takes very seriously its obligation to assess and declare any actual or potential conflicts of interest. The decision to publish or withhold such information will be made by the Editors. Acknowledge all sources of financial support. The first named author is responsible for ensuring that all authors have seen, approved and are fully conversant with its contents. The Journal accepts the criteria for authorship proposed in the *British Medical Journal* (*BMJ* 1994; **308**: 39–42). If a paper has more than six authors you should justify the inclusion of all names. Results of multicentre studies should be reported under the name of the organizing study group. Methods of recognizing contributors have been proposed (*Lancet* 1995; **345**: 668).

Disks

Following final approval of articles you must submit the accepted version on disk. IBM-compatible disks would be preferred (3½ inch). An accurate hard copy must accompany each disk, together with details of the type of computer used, software and disk system. **Do not justify.** Please send us digital versions of your figures. Ideally these should be sent in native format or WMF if created in Windows. Files saved as PS, EPS, GIF and TIF may also be used, but please note that it may not be possible to modify them. Disks will not be returned to authors.

Rejected manuscripts and illustrations will not normally be returned.

Ethics

Material relating to human investigation and animal experiments must comply with and be approved by local ethics committees. It must conform to standards currently applied in the country of origin. The Journal reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached. Written consent must be obtained from the patient, legal guardian or executor for publication of any details or photographs that might identify an individual. Submit evidence of such consent with the manuscript.

Preparation of manuscripts

The *British Journal of Surgery* subscribes to the policy of uniform requirements for manuscripts which facilitates resubmission of papers to journals without extensive recasting. Authors are advised to consult the *New England Journal of Medicine* (*N Engl J Med* 1997; **336**: 309–15), or obtain 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £2·95 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. **When quoting specific materials, equipment and proprietary drugs you must state in parentheses the brief name and address of the manufacturer.** Generic names should normally be used.

Original articles

Original articles should normally be in the format of introduction, patients and methods, results and discussion. Please provide a 200-word structured abstract. Lengthy manuscripts will be returned for shortening. The discussion in particular should be clear and concise and limited to matters arising directly from the results. Avoid discursive speculation. **Randomized clinical trials** should be clearly identified as such in the title and abstract.

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The Editorial Board of The *British Journal of Surgery* encourages submission of review articles on topics of interest. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

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The Editors commission leading articles that are 600–900 words in length and address controversial topics of current interest. They should be supported by no more than ten key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

Correspondence

The Editors welcome topical correspondence. Letters should not exceed 250 words and should be typed double-spaced.

Typescripts

Manuscripts must be clearly reproduced with adequate space for editorial notes. Present the text on one side of sheets of A4 paper (210 × 297 mm) with double spacing and 4-cm margins. **Begin each section (abstract, introduction, patients and methods, results and discussion) on a new page. Manuscripts that do not conform to these requirements will be returned for recasting.**

Title page

On the title page give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) **the name, postal and email addresses, telephone and facsimile numbers of the author responsible for correspondence and to whom requests for reprints should be addressed;** (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, review, etc).

Abstract

This must not exceed 200 words and should be presented in a structured format. **Background:** state why the study was done and its main aim. **Method:** describe patients, laboratory material and other methods used. Clearly identify the nature of the study, i.e. randomized controlled trial, retrospective review, experimental study, etc. **Results:** state the main findings including important numerical values. **Conclusion:** state the main conclusions but controversial or unexpected observations may be highlighted.

Tables and illustrations

Submit four copies of all illustrations and tables. Type each table on a separate page with a brief title. Line drawings are acceptable as clear black on white graphics, computer print-out or photocopies. Submit radiographs, photomicrographs, etc unmounted in the form of glossy prints, original transparencies or negatives. Illustrations in colour are encouraged and will be printed at no cost to the author. If you include photocopies, they should be of sufficient quality to enable the Journal's referees to judge their content and value. Label each illustration on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); indicate the top of the illustration. Include a measure of magnification of photomicrographs. Include explanations of symbols and shading within the figure. Survival curves must be accompanied by a table giving the actual numbers of patients involved. Include in the legends to illustrations and the footnotes to tables brief but comprehensive explanations of all the information presented. Look at recent issues of the Journal for examples of accepted layout. Any table or illustration reproduced from a published work must give the original source in full. You must obtain permission from the original author and the publisher before submission.

Abbreviations

Use abbreviations *sparingly*. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension. Abbreviations must be used consistently and must be defined on first use.

Numbers and units

Use the decimal point, not a comma, for example 5·7. Use a space and not a comma after thousands and multiples thereof, for example 10 000. Use SI units (International System of Units) except for the measurement of blood pressure (mmHg).

Statistics

For detailed guidance on the handling of statistical material consult *Br J Surg* 1991; **78**: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, the chosen end-points and justify the sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (*JAMA* 1996; **276**: 637–9).

Presentation

Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished and presented in parentheses after the mean values.

Analysis

Clearly describe methods used for each analysis. Methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value. Actual *P* values should be reported to two decimal places, especially when the result is not significant. The results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Take great care in your interpretations. Do not place undue emphasis on secondary analyses.

References

Type the references with double spacing in the Vancouver style (see **Preparation of manuscripts**). Reference to abstracts and personal communications is discouraged. Reference to unpublished communications will not be accepted.

In the text, number references consecutively by superscript:^{1} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence.

Leading article

The effect of litigation on surgical practice in the USA

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In order to understand the effect of the litigation system in the USA on all aspects of our society, one must appreciate that attorneys refer to our system not as the 'Justice System' but as the 'System of the Laws'. This is because our system is intrinsically adversarial, sharing only a few of the characteristics of the investigative magistrate and judge fact finding system prevalent in continental Europe. In the USA, fact finding is carried out by adversarial teams of attorneys. Indeed, facts may vary according to the skill of the attorneys representing either plaintiff or defendant.

With respect to surgical practice, litigation is commonly referred to as 'malpractice'. This is an unfortunate term; professional liability would be better known as 'practice below an accepted standard'. Most studies indicate that most 'malpractice' suits have little relationship with error, especially in the hospital setting. Indeed, most errors do not result in litigation. Conversely, most litigation has very little to do with errors, merely unfortunate outcomes and, as has become increasingly clear, failure of communication between doctor and patient. Doctors who fail to communicate adequately with patients and families are much more likely to be involved in a professional liability action than those who communicate successfully, no matter how unfortunate the clinical outcome.

In the USA, there is a central repository known as the National Practitioners Data Bank (NPDB), which lists all practitioners for whom payment is made for 'malpractice'. This is an imperfect structure that was originally intended to prevent 'bad doctors' from moving from state to state. This function of the NPDB has been rendered obsolete by the close communications that now exist between state licensing boards. It is now an electronic system from which an enquiry must be made every 2 years by hospitals before reappointment of staff, and is increasingly used by managed care organizations to restrict the size of their panels based on a physician or surgeon listing in the NPDB. This is particularly unfortunate as the system is grossly imperfect for several reasons.

1. The degree of reporting varies widely from state to state and from hospital to hospital. Two-thirds of hospitals have no reports in the past 10 years.
2. There is no threshold. Even minuscule payments (which are widely interpreted as being the price of doing business) and settlements from insurance companies when the amount settled is far exceeded by the amount to try the case are listed.
3. At least 1200 residents appear in the NPDB, despite the fact that they had no final responsibility for the care of patients.
4. The software used by the NPDB cannot differentiate reports of separate clinical incidents from multiple reports on a single incident for any given physician. Consequently, some doctors are unfairly listed within the NPDB twice owing to entries from two different payment entities on a single event.
5. At present, 16 per cent of all US doctors are listed in the NPDB. This implies that at least one-sixth of clinicians are practising below an acceptable standard. If this is indeed the case, we are in serious difficulty.

Despite these imperfections, the NPDB is taken very seriously and is now to be joined by a 'health integrity fraud data bank' that is intended to list practitioners found guilty of civil or criminal offences that do not result in professional liability payment.

One might have hoped that litigation in the USA might at least have resulted in a more informed patient population. This does not appear to be the case. For one thing, there are limits to what patients are able to absorb during the procedure we know as 'obtaining informed consent'. Various studies have shown, once it is decided that the patient will be operated on, that very little of what the surgeon explains is absorbed by the patient or family. When one asks the patient 6 months later whether any of the (audiotaped) material was mentioned, he or she often denies ever hearing it, despite its taped presence. Therefore, many physicians and most surgeons have come to practise what is called 'defensive medicine'. Being unable to document that proper consent was obtained, except by the cumbersome system of taping which itself is not without medicolegal danger, they instigate an excessive number of tests and both non-invasive and invasive preoperative procedures in an attempt to protect themselves from litigation. Very often sophisticated radiological procedures are involved. Computed tomograms replace radiological or fluoroscopic procedures, and magnetic resonance images replace com-

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This is the first of three leading articles on litigation and surgery. Next month the UK position is examined. The final article deals with Continental Europe puted tomograms. Non-invasive procedures are themselves at times replaced by invasive procedures, resulting in increased risk to the patient. Excessive laboratory tests are ordered in an effort to cover every possible exigency before operation. The costs arising from this defensive practice are difficult to estimate.

Defensive medicine is, of course, not limited to the field of operative surgery. It finds its way into every aspect of care, with increased expense. Consider, for example, the widespread practice of obtaining a computed tomogram for neck injuries in addition to standard radiographs, despite the demonstration that such imaging adds value in only 12 per cent of cases. Several years ago, the total cost of 'direct practices' of defensive medicine was estimated at US $60 billion out of a US $1·1 trillion total health care expenditure. It is likely to be higher.

It may strike the outside observer as bizarre that, at a time when there are widespread attempts to cut health care costs, this aspect of excessive costs has not been addressed. Numerous tort reform laws have been passed in the USA and the most important tort reform is the mandatory cap on non-economic 'pain and suffering' damages. However, in many states these tort reforms have been rendered void as it has been held that it is unconstitutional to place dollar limits on awards. That they are repealed in this way should be no surprise; many state supreme courts are occupied by previous trial lawyers. The effects of such tort reform and its nullification by declaration of unconstitutionality in my own state of Ohio is shown in *Fig. 1*. One can see that when the initial tort reform law in Ohio was declared unconstitutional, our payments soared from increased lawsuits for professional liability. No significant national tort reform can be expected during the Clinton administration which, while it may not have been purchased by the trial lawyers, is at least on long-term lease.

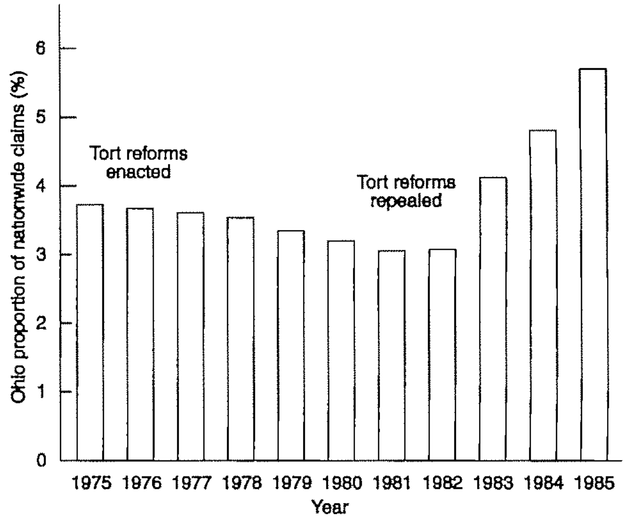

Fig. 1 Ohio adopted tort reform in 1975 when payment of medical malpractice claims in that state represented 3·7 per cent of the total paid out nationwide. That percentage declined to 2·9 per cent by 1982 but in that year the Ohio Supreme Court invalidated the US $250 000 cap on 'pain and suffering'. By 1985 Ohio's proportion of nationwide claims had risen to 5·4 per cent. Reprinted with permission from MICRA Information, January 1, 1993. Original data from Tillinghast. Copyright 1993 Californians Allied for patient protection (Capp), Sacramento, California

As increasing numbers of doctors are listed in the NPDB and the proportion approaches 25 per cent of all practitioners, the stigma will be lessened. They will then be less likely to be barred from managed care organization panels; managed care organizations are, in any event, under sharp attack by patients, the public at large, and state and national legislatures. In partial response, panels are likely to become less restrictive. As an increasing number of studies demonstrate that 'malpractice' suits and practice below the accepted standard have only a weak correlation, and confirm that the real problem is communication, an increased emphasis is being placed on communication skills in colleges of medicine and training programmes. In colleges a new movement known as 'professionalism' is being advocated and communication skills are stressed as a major part of this initiative. In residency training, and especially in surgical training, 'competence' is being stressed. Two of the four major components include caring attention for patients and communication skills. These initiatives should improve the physician–patient relationship and make lawsuits less likely. The January Retreat of the American Board of Surgery is presently dealing with the issue of competence.

Despite all of this, at least for the present, 'malpractice' suits are on the increase and awards by juries in all torts are becoming larger. Of small solace to the surgical community is the fact that surgeons are no longer the leading defendants. Internal medicine specialists and primary care physicians have supplanted surgeons, with failure to diagnose and failure to refer the leading charges. So defensive medicine continues, and tests and studies to pre-empt lawsuits increase and become ever more complex and expensive. A reasonable estimate of the expense incurred is between US $80 and 100 billion, the proper use of which could care for most of our uninsured.

What a waste.

The 'foreign' author

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Throughout the history of medicine several languages have been the 'lingua franca'. English is likely to remain the language of medicine and science despite the fact that more people worldwide speak Chinese, Hindi or other languages. The main reasons are the ease of learning and understanding basic English, the predominance of English usage in the medical community, the role of English as the main language on the Internet and in electronic and traditional publishing. Here, the 'foreign' author is therefore defined as one whose mother language is not English.

Why English?

Why does a 'foreign' author want to publish in English? The answer to this question is simple: no one in the scientific world publishes data for the unselfish purpose of advancing science and medicine alone. There are always more reasons for publishing, the most important being promotion in one's own academic career. A French, German or Japanese surgeon who has produced new and important data could be called 'naive' or even 'silly' by friends and colleagues if the article were sent to a national journal. Studies by the Institute of Scientific Information have shown that the majority of all scientific literature is written and published in English and that the English language literature is by far the most cited. According to impact factor ratings, an English publication will be cited on average 3·7 times, whereas German, French and Japanese publications will be cited only 0·6, 0·5 and 0·5 times respectively. An article written in English attracts a greater than sixfold higher response than, for example, an article written in German[1]. This means that the diffusion of knowledge and the recognition of the authors among peers are greatly enhanced if the work is published in English.

The foreign author who knows English

Speaking and writing proper English is therefore a prerequisite for making a straightforward academic career for almost all non-English-speaking scientists. Many promising academic surgeons from non-English-speaking countries spend time in hospitals or research centres in the USA, UK or Canada and have an opportunity to learn (medical) English. For most, reliance on remembered school English is often insufficient to allow fluent speech or writing in English.

The 'foreign' author should always ask a native English-speaking colleague to review the final draft of a manuscript, especially first papers. An acknowledgement at the end of the article should be sufficient to thank the colleague for efforts in simple translation.

The foreign author who does not know English

The 'foreign' author who has not expanded language skills beyond basic English always has to rely on a colleague to translate the article or on a professional translator. The first choice is undoubtedly the best. Experiences with commercial translators may be disappointing, expensive, and the meaning and message of the manuscript may be altered or lost in the translation, simply because most translators lack adequate comprehension of medical subtleties. A further problem is the secretarial task. The surgeon writer may not be capable of typing or may have to ask for secretarial assistance, for which the same language problems might arise. Perfectly bilingual secretaries are more scarce than perfectly bilingual surgeons.

Some international journals provide editorial assistance to optimize the English style of a manuscript; such an example is the *World Journal of Surgery*. This does not mean that these journals are able to rewrite manuscripts into proper English, and it is obviously very important to prepare a manuscript in the best English style possible.

While most journals do not accept or refuse papers from foreign authors on the basis of 'good' or 'poor' English, proper English does lead to easier comprehension, more effective refereeing and editing, and therefore expedites publication.

To publish nationally, internationally or both?

Most non-English-speaking authors want not only to promote their academic careers and be known internationally but also to be known and to advance in their careers in their own country, and publication in their national language is mandatory. It is still a fact that in countries with fairly large populations, such as Japan, Germany, France and Italy, most native clinicians read and gather information from journals written in their own language. The non-English-speaking author sometimes has to make a difficult decision concerning the aims and objectives of the manuscript[2]: should the paper promote the academic career and international recognition, or should it contribute to national reputation? Non-English-speaking authors may be divided into two groups: those who publish exclusively in their native language, achieve an average or below-average academic career and work in a non-academic or teaching hospital. The second group is composed of those who place publications both internationally and nationally; these surgeons usually become chiefs of university departments of affiliated hospitals. There are few, if any, who will publish exclusively in English. This is true for basic scientists only.

There are important economic and academic considerations from the perspective of national non-English journals. If authors send all good manuscripts to English journals, the national language publications may wither as they publish only second-class original data or review papers only. National journals try to overcome this situation by providing excellent English abstracts and listing in international publication retrieval systems. In the near future, electronic publication of an English translation of the full text may be practical and, in this way, duplicate publications will also disappear.

In order to avoid the decline or wither dilemma, the publishers of *Langenbecks Archiv für Chirurgie*, a German-language journal founded in 1860, decided in 1998 to publish exclusively in English. The hope was to increase the impact factor (which indeed happened) and to attract good manuscripts from German authors who would otherwise have sent material to 'English' journals. Time will show whether the journal succeeds in this effort.

Duplicate publication in a foreign language: is it redundant?

Previously some authors have published the same material concurrently in their national language and in English because of the difference in impact factors of the respective journals and insufficiencies in the indexing system. In the electronic age this is no longer possible as the new databases will index practically all articles (usually with an English translation of the title). If potential (foreign) authors continue to do this without informing the editors of both journals, they fulfil the criteria for duplicate publication, a serious and dishonest situation which is rightly viewed as a publishing misdemeanour. The present authors think that this problem should be eliminated by discussion and agreement among established editors of the most important medical journals worldwide. The Vancouver group[3] in 1997 published prerequisites that would allow duplicate publication, particularly in two different languages. The conditions that should be met are[3]:

- 'The authors must have received approval from the editors of both journals. The editors concerned with secondary publication must have a photocopy, reprint or manuscript of the primary version.
- The priority of the primary publication is respected by a publication interval by at least one week (unless specifically negotiated otherwise by both editors).
- The paper for secondary publication is intended for a different group of readers; an abbreviated version would be sufficient.
- The secondary version reflects faithfully the data and interpretation of the primary version.
- A footnote on the title page of the secondary version informs readers, peers and documenting agencies that the paper has been published in whole or in part in the primary reference. A suitable footnote might read: "This article is based on a study first reported in: (title of journal, with full reference)."
- Permission for such secondary publication should be free of charge.'

If journals worldwide would agree to these conditions, non-English-speaking authors would be freed from a dilemma: should I publish important data in a national language journal of which my peers outside the country will not take note with almost no impact points, or should I publish in an English journal with gain of more impact points for my academic career even though my national peers and national institutions will not be aware of the paper? English-language journals should accept the above-mentioned conditions and should not always demand to be the principal journal for publication, relegating the national journals to second position.

Finally, important papers in national (non-English) journals do not easily find the correct path to the citation index or into overviews and meta-analyses (Egger Lancet 1997). This deficit should hopefully be overcome in the latest electronic publishing era.

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3 International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *N Engl J Med* 1997; **336:** 309–15.

Committee on Publication Ethics

GUIDELINES ON GOOD PUBLICATION PRACTICE

9 Media relations

Definition

Medical research findings are of increasing interest to the print and broadcast media. Journalists may attend scientific meetings at which preliminary research findings are presented, leading to their premature publication in the mass media.

Action

1 Authors approached by the media should give as balanced an account of their work as possible, ensuring that they point out where evidence ends and speculation begins.
2 Simultaneous publication in the mass media and a peer reviewed journal is advised, as this usually means that enough evidence and data have been provided to satisfy informed and critical readers.
3 Where this is not possible, authors should help journalists to produce accurate reports, but refrain from supplying additional data.
4 All efforts should be made to ensure that patients who have helped with the research should be informed of the results by the authors before the mass media, especially if there are clinical implications.
5 Authors should be advised by the organisers if journalists are to attend scientific meetings.
6 It may be helpful to authors to be advised of any media policies operated by the journal in which their work is to be published.

10 Advertising

Definition

Many scientific journals and meetings derive significant income from advertising. Reprints may also be lucrative.

Action

1 Editorial decisions must not be influenced by advertising revenue or reprint potential: editorial and advertising administration must be clearly separated.
2 Advertisements that mislead must be refused, and editors must be willing to publish criticisms, according to the same criteria used for material in the rest of the journal.
3 Reprints should be published as they appear in the journal unless a correction is to be added.

Other sections of these guidelines will appear in future issues. The full guidelines are available at http://www.publicationethics.org.uk

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Clinical dilemma

A problem bile duct stone

During routine laparoscopic cholecystectomy, cholangiography reveals a gallstone in an otherwise normal bile duct. How should this situation be managed? Professor Robrecht Van Hee of Antwerp discusses the background of such a clinical dilemma and suggests how the situation might be assessed and handled.

In 1·2 per cent of cases[1] the laparoscopic surgeon performing routine cholangiography during laparoscopic cholecystectomy is confronted with an unexpected stone within a normal calibre common bile duct (CBD). The frequency of such a finding is related to the extent of preoperative assessment. In most countries, a clinical history and examination is followed by laboratory tests that include determination of serum bilirubin, alkaline phosphatase, γ-glutamyl transferase and transaminases, and by abdominal ultrasonography. If these different examinations remain negative with respect to the presence of CBD stones, further preoperative assessment is usually not indicated.

The overall prevalence of CBD stones in patients with cholelithiasis has dropped from 15 per cent in the era of open surgery to 6 per cent[2] in the laparoscopic era. Still, 6 per cent is important and some authors continue to advocate the use of intraoperative cholangiography[3]. On the other hand, as good to excellent results can now be achieved after postoperative sphincterotomy and stone extraction, others have deleted intraoperative cholangiography from their practice during laparoscopic cholecystectomy, preferring to treat CBD stones in the postoperative phase. They argue that laparoscopic cholangiography offers a poor quality of image, causing frequent false-positive cholangiograms which induce unnecessary CBD explorations. Such explorations in turn prolong the operation time and increase costs[4]. The counter argument is that the operation time is increased by a mean of only 6·9 min without any statistically significant increase in morbidity or mortality rate[5].

So if stones are found at laparoscopy, how should they be managed and what are the best and safest treatment options?

Should unexpected common bile duct stones be treated?

CBD stones usually pass into the duodenum when there is no distal biliary obstruction and so small-diameter calculi may possibly be left untreated until symptoms occur. In one series of 1050 patients subjected to laparoscopic cholecystectomy, 57 per cent had no risk signs indicating the presence of CBD stones. No patient in this group had clinical evidence of residual CBD calculi during a follow-up period of 45 months[6]. On the other hand, unknown or untreated CBD stones are frequently reported to cause complications, but this depends greatly on the age of the patient.

Younger patients (under 70 years) have more chance of developing severe complications, including acute cholangitis, pancreatitis, jaundice and bile duct fistula. Older patients (over 70 years) seem generally to be untroubled; most remain asymptomatic, probably owing to physiological dilatation of the CBD. It therefore seems sensible to treat younger patients by clearance of the CBD to prevent complications, a trend that is reflected in the recent series of Ganguli *et al.*[7]. These authors found that, whether suspected during or after operation, CBD stones have indeed induced a greater number of postoperative endoscopic retrograde cholangiographies since the introduction of laparoscopic cholecystectomy.

Should unexpected common bile duct stones be treated during the laparoscopic procedure?

Assuming one wishes to treat the stones, the question arises of whether this should be done during the laparoscopic operation or postponed for a couple of days until endoscopic sphincterotomy and stone extraction can be performed. This debate has given rise to numerous reports on the efficacy of both techniques, including randomized prospective trials designed to compare endoscopic retrograde cholangiopancreatography (ERCP) with CBD exploration. ERCP results seem poor, as stone clearance is obtained in only 76 per cent of patients at the first attempt, with a morbidity rate of 16 per cent[2]. Laparoscopic CBD exploration also achieves a low success rate of about 76 per cent, but this rises to 100 per cent after conversion to open operation of patients with more complicated dissection or laparoscopically inaccessible calculi.

Laparoscopic CBD exploration success rates vary, in one collective overview from 73 to 94 per cent, with mean operating times varying from 90 to 174 min; the mortality rate ranges from 0 to 1 per cent and the morbidity rate from 1 to 12 per cent. When laparoscopic cholecystectomy plus CBD exploration was compared with laparoscopic cholecystectomy followed by endoscopic sphincterotomy, laparoscopic transcystic CBD exploration proved to result in a shorter hospital stay. However, important factors in deciding which option to choose are the expertise of the laparoscopic surgeon and the quality of the available equipment.

The surgeon detecting CBD stones at laparoscopic cholangiography may remove calculi either by the transcystic route or by incision of the CBD. The transcystic route may be the ideal approach for smaller stones (less than 9 mm) located distal to the cystic duct. In such circumstances, extraction following dilatation of the cystic duct is feasible in 80–90 per cent of cases, with a mortality rate of 0–1·25 per cent and a morbidity rate of 5–6 per cent. For large or impacted stones, or stones proximal to the cystic duct confluence, direct CBD exploration is preferred; it can be performed with a mortality rate of 1–2 per cent and a morbidity rate of 5–7 per cent. If laparoscopic removal proves unsuccessful, the surgeon may opt either for conversion to an open procedure or for postoperative extraction at ERCP.

Does the calibre of the common bile duct influence the decision to refrain from treatment, and the choice between laparoscopic treatment and endoscopic retrograde cholangiopancreatography?

In general a normal calibre duct (less than 8 mm) reflects the presence of smaller stones that do not cause CBD obstruction and dilatation. Such stones can generally be extracted laparoscopically by the transcystic route.

If such a procedure does not succeed in CBD clearance, or if the number of stones detected at cholangiography does not exceed five or six, laparoscopic incision choledochotomy may be undertaken. However, this requires advanced laparoscopic skills, especially in a normal calibre duct. The incision is generally carried out longitudinally and may be either closed primarily or (preferably) over a T tube, allowing postoperative cholangiography. If the surgeon is not familiar with laparoscopic CBD exploration, postoperative clearance by ERCP and sphincterotomy may be sensible.

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Review

Molecular technology and pancreatic cancer

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Background: Pancreatic cancer is the fifth leading cause of cancer death in the Western world. Despite improvement in operative mortality rates, little impact has been made on overall 5-year survival. This review discusses the molecular changes peculiar to pancreatic cancer and how the use of molecular technology might affect detection, screening, diagnosis and treatment of the disease.

Methods: A literature review was performed using the National Library of Medicine's Pubmed database; this was combined with ongoing work within the Queen Elizabeth Hospital, Birmingham.

Results: Over the past 20 years great strides have been made in our understanding of the molecular basis of disease. Advances in molecular biology are now reshaping how diseases are screened for, diagnosed, investigated and treated. In recent years collaboration between clinicians and basic scientists has revealed a unique pattern of genetic and molecular events in pancreatic cancer. This review discusses how these advances may impact on patients with this disease.

Conclusion: The past decade has seen some improvement in outlook for patients with pancreatic cancer, but the 'molecular age' promises to deliver even better results.

Paper accepted 22 March 2000

British Journal of Surgery 2000, 87, 840–853

Introduction

Carcinogenesis involves the stepwise accumulation of genetic changes, associated with progression through initiation, transformation, invasion and ultimately the establishment of metastases[1]. The genetic processes leading to this progression disturb the equilibrium of a cell by altering the relative balance between the roles of the cell cycle, differentiation and dedifferentiation, and programmed cell death (apoptosis). The early stages of tumorigenesis usually involve the functional loss of one or more tumour suppressor genes (involved in the control of the cell cycle) by a mutation or deletion. Subsequently, there is activation of proto-oncogenes (which transcribe growth factors), growth factor receptors and second messenger systems, by specific mutations that control cellular activity and differentiation. These, along with tumour suppressor genes, affect apoptosis. Pancreatic cancer is unusual because an oncogene mutation (K-*ras*) appears to precede all other genetic events[2–4].

The development and growth of pancreatic cancer follows this general model, but a particular genetic profile appears to distinguish pancreatic ductal adenocarcinoma from other epithelial tumours of the gastrointestinal tract (*Fig. 1*). Pancreatic cancer has a high incidence of alterations in the K-*ras* oncogene[5–9] (*Table 1*)[2,5,7–16] and the *p53*, *p16* and *DPC4* tumour suppressor genes[17–20] (*Table 2*)[14,15,19–28]. Each oncogene and tumour suppressor gene identified represents a potential difference between pancreatic cancer and normal or inflammatory pancreatic tissue. This difference may potentially be useful, either as a novel target for therapy or to discriminate between benign and malignant tissue[29].

Detection of inherited predisposition

A familial predisposition to pancreatic malignancy, either alone[30] or in association with other malignancies, is now well established (*Table 3*)[31–48].

Several groups of patients have an increased risk of pancreatic cancer; the bulk of these patients are in families with what appears to be a site-specific cancer phenotype without the identification of a chromosome linkage[31,36,41,49–53]. Continued molecular investigation of these families may yield a group of patients with a defined chromosomal linkage and lead to the discovery of specific gene loci.

Patients in whom a defined genetic abnormality has been identified that predisposes to pancreatic cancer are the most interesting but they are also the most unusual. The *p16* tumour suppressor gene is mutated in families with the familial atypical mole and melanoma syndrome, which in

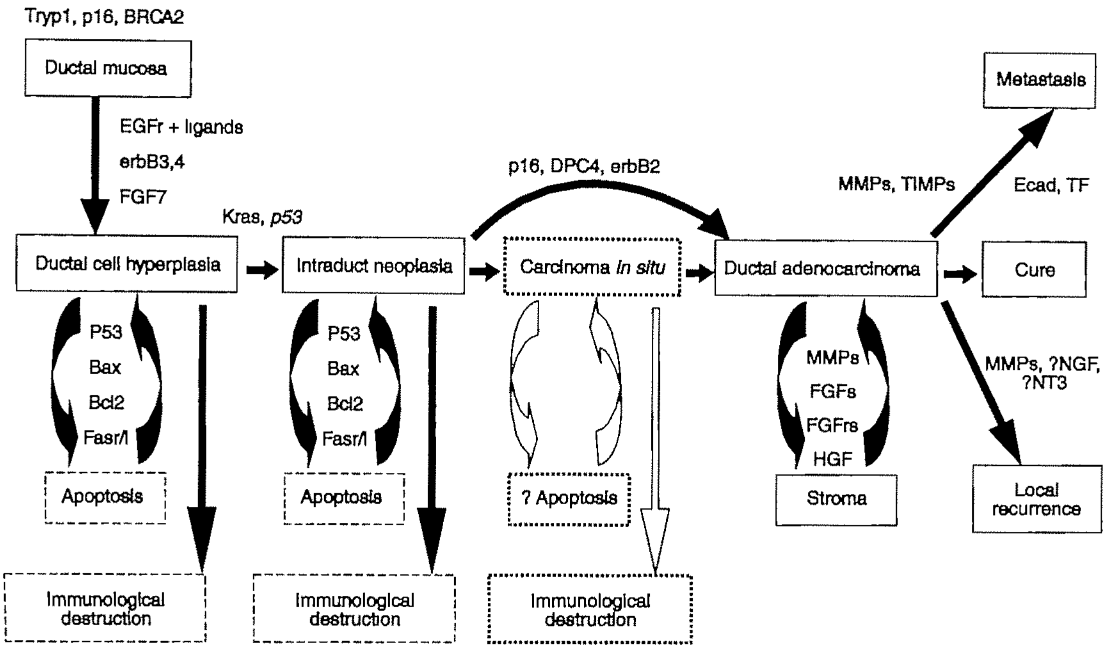

Fig. 1 Molecular cascade for pancreatic carcinogenesis. MMP, matrix metalloproteinase; TIMP, tissue inhibitor of MMP; TF, tissue factor; Ecad, E-cadherin; NGF, nerve growth factor; NT3, neurotropin 3; EGF, epidermal growth factor; Fasr/l, Fas receptor ligand; FGF, fibroblast growth factor; FGFr, fibroblast growth factor receptor; HGF, hepatocyte growth factor

Table 1 K-*ras* mutations in pancreatic ductal adenocarcinoma

Reference	Year	No. of patients	Frequency of mutation
Almoguera *et al.*[10]	1988	22	21 (95)
Smit *et al.*[11]	1988	30	28 (93)
Grunewald *et al.*[5]	1989	65	49 (75)
Mariyama *et al.*[7]	1989	13	10 (77)
Shibata *et al.*[8]	1990	27	20 (74)
Tada *et al.*[12]	1990	18	18 (100)
Montijima *et al.*[13]	1991	40	35 (88)
Lemoine *et al.*[2]	1992	16	12 (75)
Hruban *et al.*[9]	1993	82	68 (83)
Pellegata *et al.*[14]	1994	35	25 (71)
Dergham *et al.*[15]	1997	76	64 (84)
Banerjee *et al.*[16]	1997	15	15 (100)
Total		439	365 (83)

Values in parentheses are percentages

Table 2 *p53* mutations in pancreatic ductal adenocarcinoma

Reference	Year	No. of patients	Frequency of mutation
Barton *et al.*[23]	1991	22	13 (59)
Ruggeri *et al.*[24]	1992	136	76 (56)
Scarpa *et al.*[25]	1993	34	14 (41)
Casey *et al.*[26]	1993	34	16 (47)
Zhang *et al.*[27]	1994	19	10 (53)
Pellegata *et al.*[14]	1994	35	18 (51)
Dergham *et al.*[15]	1997	76	33 (43)
Kasuya *et al.*[28]	1997	70	43 (61)
Total		426	223 (52)

Values in parentheses are percentages

some cases seems to be associated with an increased risk of pancreatic cancer[40,41,54,55]. Affected individuals from kindreds with hereditary pancreatitis are also at increased risk of the disease[56]. Whitcomb *et al.*[57] reported that an Arg–His substitution at residue 117 of the cationic trypsinogen gene is associated with the hereditary pancreatitis phenotype in these kindreds. The gene was subsequently identified by the same group[58]. The cumulative risk of developing pancreatic cancer in these kindreds is believed to be 40 per cent up to the age of 70 years[56]. *BRCA2* gene mutations occur in families with breast and ovarian cancer, and such families have recently been shown to demonstrate an increased risk of developing pancreatic cancer[59]; loss of heterozygosity has been demonstrated at the *BRCA2* locus in spontaneous pancreatic cancer[60].

Molecular technology and the implications for clinical practice

The number of patients with an inherited predisposition to pancreatic cancer is small, but there is a potential both for

Table 3 Inherited syndromes possibly associated with pancreatic cancer

Reference	Year	Syndrome	Inheritance	Other tumours
Ehrenthal *et al.*[31]	1987	Familial pancreatic cancer	Not known	—
Comfort and Steinberg[32]	1952	Hereditary chronic pancreatitis	D	—
Jagelman *et al.*[33]	1988	Familial adenomatous polyposis	D	Colon, duodenum, small bowel, liver, biliary tract, ampulla of Vater, thyroid, brain, desmoid
Giardiello *et al.*[34]	1987	Peutz–Jeghers	D	Small bowel, colon, duodenum, stomach
Lynch *et al.*[35]	1985	Lynch II	D	Colon, ovary, uterus, bladder, breast, stomach
Danes and Lynch[36]	1982	Familial colonic and pancreatic cancer	?D	Colon
Taylor[37]	1992	Ataxic telangiectasia	R	Lymphocytic leukaemias, lymphoma, lung, breast, gallbladder, stomach

D, autosomal dominant; R, autosomal recessive

early detection and therapy in such patients. The cumulative lifetime risk for those with this disparate group of hereditary conditions could be between 40 and 75 per cent[56]. The identification of families and careful screening for known genetic mutations should allow genetic counselling of affected individuals and the targeting of interventional screening tests to an appropriate population. Current therapy for affected individuals would still be prophylactic pancreatectomy, or endoscopic polypectomy in patients with familial adenomatous polyposis, but the replacement of mutated or lost tumour suppressor genes by gene therapy techniques may be possible in the future[61].

Screening

Improvement in survival for patients with pancreatic cancer might be achieved by early surgery[62–64]. Resection rates for affected patients are generally poor[65–67], but rates of over 40 per cent can be achieved without any means of early diagnosis[68]. If tumours could be diagnosed when 1 cm or less in size, resection rates of over 90 per cent might be attainable, with the potential for a concomitant increase in 5-year survival[69].

There is no ideal serum screening test yet available. All currently tested tumour markers lack the sensitivity required for general use when used alone, and there is little evidence that an improved sensitivity and specificity can be achieved by combination of markers[70]. Radiological cross-sectional imaging (computed tomography (CT) and magnetic resonance imaging (MRI)) might have the required sensitivity (detection of lesions of 1 cm or greater) as a screening tool but can be ruled out on cost grounds; ultrasonography does not have the required sensitivity when used alone[71].

Cytological examination of duodenal aspirates has diagnostic limitations because cells are rapidly degraded by enzymes within the duodenal lumen, which complicates cytological interpretation[72–74]. Pure pancreatic juice obtained at endoscopic retrograde cholangiopancreatography (ERCP) has also been studied but, although cell morphology is well preserved in pancreatic juice, cytological diagnosis of pancreatic cancer is only achieved in 30–79 per cent of cases[72,75].

Molecular advances

The development of DNA amplification by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) has greatly facilitated the detection of K-*ras* mutations[76,77]. Since these techniques are highly specific and can detect one in 100 000 copies of mutant K-*ras* genes in the presence of normal alleles[78], only a very small number of cells containing the mutation is required for their detection. PCR and RFLP will detect K-*ras* mutations affecting the first two bases of codon 12 and this is a useful primary test for screening a large number of tumours quickly; it will detect most (75–93 per cent) K-*ras* mutations[79]. The amplification refractory mutation system (ARMS; Zeneca Diagnostics, Maccelsfield, UK) is a mutant-specific amplification-based technique that allows the detection of sequence changes occurring at codon 12[80] and should yield a sensitivity of 100 per cent.

The preservation of sufficient telomere length is necessary for cellular immortalization. Most somatic cells lack telomerase activity so that gradual shortening of the telomere occurs with each cell division, ultimately leading to cell death[81]. The repression of such activity that is seen in normal somatic cells is lost in many cancer cells; telomerase activity is detectable, leading to cellular immortality[82]. Telomerase activity has been detected in 95 per cent of pancreatic cancer specimens and in a smaller proportion of pancreatitis specimens, but not in normal controls[83].

Normal (wild type) *p53* is not usually detectable, but mutant *p53* has a much longer half-life resulting in its accumulation within the nucleus where it is detectable by immunohistochemistry[23,84,85]. Wild-type *p53* is involved in cell cycle regulation and apoptosis and so under certain circumstances expression may be transiently increased; while increased *p53* immunoreactivity usually represents mutant *p53* expression, under certain conditions this may not be so. This problem reduces the usefulness of *p53* as a specific diagnostic marker for pancreatic malignancy when used alone. The only certain means of discriminating between wild-type and mutant *p53* is by mutation analysis.

Targeted screening

Screening may become routine for members of familial pancreatic cancer families and for those with a known and considerably increased risk of cancer (e.g. those with diabetes mellitus). At least 20 per cent of patients with pancreatic cancer have a diagnosis of diabetes mellitus at presentation[86] and this may precede the diagnosis of cancer, by up to 2 years[87]. It is estimated from West Midlands (UK) data that one in 45 newly diagnosed diabetics will develop pancreatic cancer within 2 years of diagnosis. The cancer detection rate could be increased if newly diagnosed diabetics over the age of 45 years, with no family history of diabetes and who are not obese, are chosen as the population for screening.

Molecular technology and the implications for clinical practice

With current technology, endoscopy, and either duodenal or pancreatic secretion sampling, cannot be recommended as a screening test. It may be possible, however, to use such techniques in addition to K-*ras* mutation analysis and *p53* immunohistochemistry in targeted populations, for those patients in whom diagnostic doubt exists.

K-*ras* mutations have been detected in the pancreatic duct aspirates of most patients with adenocarcinoma of the pancreas and have not been reported in patients with benign pathology[79, 88–90]. Detectable telomerase activity has been reported from pancreatic ductal cells obtained during ERCP by cytological brushing in patients with pancreatic cancer, but it is not detected in those with benign pancreatic disease[91]. K-*ras* mutations have also been detected in the stools of patients with adenocarcinoma of the pancreas, but not in those of patients with chronic pancreatitis[92]. The application of stool DNA analysis as a screening tool has potential in the management of gastrointestinal tract tumours; pancreatic cancer has a particularly high incidence of K-*ras* mutations. Current technology allows the detection and amplification of human DNA in approximately 90 per cent of stool samples, a proportion that may be improved with increasing expertise in this area.

Diagnosis

In the past decade there have been important advances in imaging techniques, particularly in the areas of spiral CT, MRI and positron emission tomography. Despite these advances and concomitant improvements in ERCP, radiologically guided biopsy and serological markers, all techniques are still limited in their sensitivity and specificity. Even in combination, 100 per cent sensitivity and specificity cannot be achieved[93].

Most patients with pancreatic cancer present with advanced inoperable disease[65] which rarely causes a diagnostic dilemma. Some, however, present with a pancreatic mass that is technically resectable (and so they are potentially curable) but in whom there is doubt about the diagnosis. The diagnosis will only be established for a proportion of patients after resection, when definitive histology is available. The emerging molecular characteristics of chronic pancreatitis mean that it may be possible to use the molecular differences between chronic pancreatitis and pancreatic cancer to differentiate the two conditions.

Molecular technology and the implications for clinical practice

K-*ras* mutation analysis of pancreatic juice could be used to help discriminate chronic pancreatitis from pancreatic cancer[94,95]. The diagnosis of pancreatic cancer by fine-needle aspiration cytology (FNAC) has a sensitivity of 90 per cent in the best hands[96], but difficulty can occur in those with inflammatory atypia, which may be difficult to distinguish from well differentiated adenocarcinoma. The addition of K-*ras* mutation analysis to standard FNAC can increase its sensitivity from 69 to 92 per cent[97,98], and the investigation can be completed reliably within 48 h without special handling[99].

The developing molecular characteristics of pancreatic cancer have highlighted a number of genetic abnormalities that can be detected in the serum. Mutant *p53* can be detected in the circulation using antibodies[100,101] but, despite a high specificity for pancreatic malignancy, its sensitivity of only about 20 per cent reduces its clinical value as a tumour marker[102].

Many growth factors and growth factor receptor systems are altered in the development of pancreatic cancer yet few appear likely to add substantially to the diagnostic pathways of the disease. This may in part be due to the variability of expression of these systems and in part to the relative lateness of their recruitment down the tumorigenesis pathway (*Fig. 1*). Several systems have, however, been proposed as prognostic indicators and can be assayed using relatively simple immunohistochemical techniques[103,104].

Treatment

The overall 5-year survival of patients with pancreatic cancer is less than 1 per cent and has changed little in the past 20 years[65,66,105,106]. Despite the substantial improvements that have occurred in the diagnosis and treatment of the disease during this time, over 95 per cent of patients die from their pathology within 5 years. The poor response to conventional therapy and the almost unique molecular make-up of pancreatic cancer has led scientists and clinicians to develop novel therapeutic approaches.

Molecular technology and the implications for clinical practice

Gene replacement

In vitro gene replacement may achieve dramatic antitumour effects[107–109], but conversion of this technology into a clinical strategy has been beset with difficulty[110]. Neoplasms almost always accumulate a series of genetic mutations during tumorigenesis, and during transformation several subclones of tumour cells develop, some of which may have a very different genetic make-up. Individual genetic abnormalities are often only important at specific points during tumour evolution, suggesting that replacement of gene function as a therapeutic strategy may have only a narrow therapeutic window.

Inactivation of the *p53* tumour suppressor gene by a point mutation is the most frequent genetic event in human malignancy. It occurs with a frequency of about 60 per cent in tumours of the colon, breast, lung, liver and pancreas[23,111–114] and has been most extensively studied in gene replacement therapy strategies. The *ex vivo* introduction of wild-type *p*53 into tumour cells that express the mutant variant can suppress the malignant phenotype both *in vitro* and *in vivo*[115,116]. Replication-incompetent adenoviruses have been used to deliver wild-type *p*53 into a variety of tumour types[117–122].

Replacement of defective tumour suppressor gene function by homologous recombination can be achieved *in vivo*, but the process is very inefficient in mammalian cells[123]. Even when conditions are favourable, *in vitro* transfection occurs in only 10–30% cells; it is therefore unlikely that this approach would work *in vivo* with an established tumour mass[110]. However, it is possible that such an approach might be used to replace defective genes in preneoplastic cells in patients with a hereditary predisposition to pancreatic cancer. Alternatively, this technique might potentiate more conventional therapies. Chemotherapy and radiotherapy rely on the induction of apoptosis, and recent studies have shown that their effectiveness may be partly dependent on the *p53* status of the targeted tumour cells[124].

Genetic prodrug activation therapy

Genetic prodrug activation therapy (GPAT) utilizes differential transcription between normal and malignant cells to drive the expression of genes that confer selective sensitivity to a prodrug (*Fig. 2*). These 'suicide genes' are invariably derived from a non-mammalian system. Four major enzyme systems have been studied as prototypes for GPAT.

Herpes simplex thymidine kinase converts the relatively non-toxic ganciclovir into its monophosphate form, which is further metabolized by cellular kinases to diphosphate and triphosphate forms[125]. The diphosphate and triphosphate forms of ganciclovir cause DNA chain termination which, both *in vitro* and *in vivo* (using human pancreatic cancer xenografts in nude mice), produces a dramatic reduction in peritoneal metastases[126,127]. Since these results have also been recorded in several other tumour models, this technique remains a novel potential treatment[128–130].

The *Escherichia coli* nitroreductase enzyme DT diaphorase can reduce the relatively weak alkylating agent CB1954 (5-(aziridin-1-yl)-2,4-dinitrobenzamide) to a potent bifunctional alkylating agent[131,132]. The human and murine forms of DT diaphorase are deficient in this reaction[133]. The active drug generated by the nitroreductase system is up to 100 000 times more cytotoxic than the prodrug[134]. This species difference can be exploited by forced expression of the 'suicide gene' by cancer cells[135].

Cytosine deaminase (present in *E. coli*) will convert the relatively non-toxic 5-fluorocytosine to 5-fluorouracil, which is further converted intracellularly to 5-fluorouridine 5′-triphosphate and 5-fluoro-2′-deoxyuridine 5′-monophosphate[136,137]. These active metabolites interfere with both RNA and DNA synthesis, eventually leading to cell death. These features are being exploited in GPAT techniques[138].

All of these 'suicide' strategies rely on differential expression of the genes in malignant and normal cells. Differential expression can be achieved in several ways, using either direct injection, transductional or transcriptional targeting. Transduction relies on the preferential delivery of genes to the target cells by phenotype selection. Selection may be very simple, such as targeting a rapidly dividing tumour within a quiescent host organ, or by using

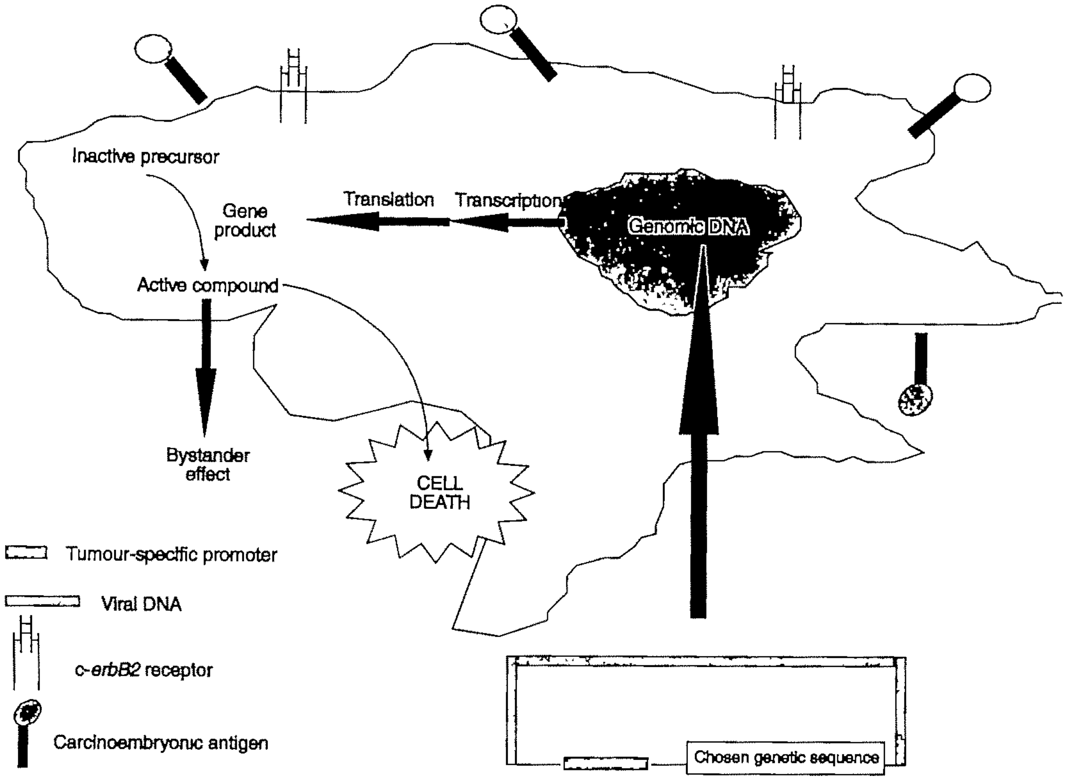

Fig. 2 Genetic prodrug activation therapy

antigen/antibody targeting or similar types of system. Transcriptional targeting relies on specific differences in expression of tumour-specific transcriptional elements in malignant and non-malignant cells. The gene promoters from these upregulated transcriptional elements are inserted upstream of the suicide gene construct within the viral vector. Cells that demonstrate overexpression of the transcriptional element will necessarily overexpress the suicide gene. Several transcriptional elements have been proposed for use in this context including carcinoembryonic antigen, vascular endothelial growth factor, MUC1 and erbB2[138–141].

The problem with this approach is the limited level of gene transduction that can be achieved with current delivery systems. In optimized *in vitro* conditions, gene transduction rates of between 10 and 70 per cent can be achieved, but transduction levels *in vivo* are substantially lower[132,138,142–144]. This problem is partly countered by the bystander effect in which non-transduced cells in coculture with the transduced population are also killed (*Fig. 2*), but there is still a need to develop more efficient promoters.

Antisense, immunology and peptide technology

The *ras* family comprising the Harvey (H), Kirsten (K) and N-*ras* proto-oncogenes are the most frequently activated group of transforming genes in human cancer[145,146]. The immune system of both healthy individuals and patients with cancer has the potential to recognize and react to cells expressing *ras* mutations[147–152]. The effector cells involved in this recognition are T helper (CD4 positive) and cytotoxic T (CD8 positive) cells[148,151,153]. Both of these T-cell subsets are able to kill or inhibit growth of cancer cell lines that harbour corresponding *ras* mutations[153–155]. Synthetic *ras* oncogene peptides have been developed and tested in both preclinical and clinical studies without significant toxicity being noted (Merck KgaA, Frankfurt, Germany, unpublished data). A phase II study, designed to evaluate immunological response, is planned in patients with surgically resectable pancreatic cancer.

Protein expression of a mutant K-*ras* oncogene can be suppressed by 95 per cent *in vitro* by using antisense messenger RNA (mRNA), and this is accompanied by a reduction in cell growth[156]. Liposome-mediated gene transfer of an antisense K-*ras* construct has been used to treat murine xenografts of the human pancreatic cancer cell line AsPC-1. There was no evidence of toxicity in this animal model which showed a significant inhibition of tumour progression[157].

Mutated *p53* has also been targeted in clinical trials for antisense suppression using both exogenously supplied oligonucleotides and endogenously expressed antisense constructs. Although there has been little evidence of clinical efficacy, no toxicity has been reported[158]. This technique has also been applied *in vitro* to a pancreatic model; the antisense oligonucleotides had an antiproliferative effect but no effect on mutant p53 expression[159]. While appearing to be simple and effective, antisense technology has many deficiencies in its current form. Some of the inhibitory effects recognized using this technique may be result from binding to molecules other than mRNA, making it very difficult to determine the exact mode of action.

The polypeptide hormone gastrin has several physiological functions and is a known growth mediator of gastrointestinal mucosal cells[160,161]. The gastrin species produced by cancer cells are generally immature but gastrin-17, found in tumour cells, has proliferative effects on gastric, colon and pancreatic cancer cell lines[162,163]. Several antigastrin strategies have been employed *in vitro*, all demonstrating antiproliferative effects[160,162,164,165]. Antibodies have been raised against the amino terminal of gastrin-17 (gastrimmune), because of the three-dimensional interaction of the gastrin-17 molecule with the gastrin receptor, which blocks the amino terminal with a high-affinity antibody and prevents effective ligand–receptor association[166]. Gastrimmune has antiproliferative effects *in vitro* and in human gastrointestinal cancer xenografts[167,168], and is currently undergoing phase II trials in patients with gastric cancer. A large phase III study is planned for pancreatic cancer.

Designer drugs

The rapid increase in knowledge of the molecular and cellular biology of malignancy has enable the accurate targeting of cellular pathways with synthetic compounds to inhibit these pathways for potential therapeutic benefit. The matrix metalloproteinases (MMPs) are proteolytic enzymes, each with different substrate specificities within the extracellular matrix; they have an important role in degradation of this matrix[169]. Expression of several members of the MMP family is significantly greater in pancreatic cancer than in normal pancreas[170–172]. It is believed that an imbalance between activated MMPs and tissue-specific inhibitors leads to matrix degradation and tumour invasion. Several broad-spectrum synthetic MMP inhibitors have been developed. One of these, marimastat, has now been used in phase II and phase III clinical trials in patients with inoperable pancreatic cancer, both in the UK and USA[173]. Preliminary data from these studies have been encouraging, low toxicity and prolongation of survival being reported compared with historical controls[173].

The *ras* genes encode guanosine 5′-triphosphate (GTP)-binding proteins that have a key role in growth factor signal transduction and control of cellular proliferation. Wild-type ras protein cycles between an active GTP-bound and inactive GTP-bound state, but the products of the mutated *ras* oncogenes are locked in the active GTP-bound state. After cytoplasmic synthesis the ras proteins undergo a series of processing events culminating in membrane association. The first of these processing steps is farnesylation of the carboxy terminal cysteine residue of ras by farnesyl protein transferase (FPT)[174–177]. Inhibition of FPT prevents membrane localization and ablates the activity of the ras protein; both *in vitro* and *in vivo* studies suggest that this approach may provide a novel treatment strategy for pancreatic cancer[178–180]. Specific FPT inhibitors have been developed that block the growth properties of transformed human tumour cells *in vitro* and result in antitumour activity in animal studies (Schering Plough Research Institute, Kenilworth NJ, USA, unpublished data). One of these novel agents is currently in a phase II clinical trial in patients with advanced pancreatic cancer.

Conclusion

During the past decade there have been many advances in 'conventional' medical technology that have led to valuable improvements in the diagnosis, staging and treatment of pancreatic cancer. Over a similar period there have also been dramatic improvements in surgical morbidity and mortality rates in patients undergoing surgery for pancreatic cancer, at least partly as a consequence of greater subspecialization[181–185]. Despite these changes there have only been slight improvements in the overall survival of patients with this disease. Conventional chemotherapeutic intervention appears to be largely ineffective in the treatment of pancreatic cancer, only marginal survival benefit accruing from even the latest generation of drugs.

Over the past decade there has also been spectacular advance in knowledge of the genetic basis of cancer. This has been fuelled by rapid progress in molecular technology. Many of the problems associated with translating this expansion of knowledge to the common clinical situation relate to the great heterogeneity in molecular defects that occur within one tumour type. Pancreatic cancer is almost unique among solid gastrointestinal tumours in its frequency of genetic abnormalities, such as K-ras activation and *p*53 and DPC4 loss. These features and the dismal prognosis associated with the disease have led to the testing of novel strategies for its management.

Identification of a hereditary genetic predisposition to pancreatic cancer has led to the formation of pancreatic cancer registries around the world, with voluntary screening of patients and siblings for the hereditary genetic defect. Asymptomatic population screening remains unrealistic, but the recognition of subpopulations at increased risk from pancreatic cancer, along with novel and sensitive detection techniques, means that targeted population screening is a step closer.

A small number of specialist research laboratories have been using novel molecular techniques to improve the sensitivity and specificity of conventional diagnostic methods in patients with pancreatic disease. The use of such methods is likely to expand. Molecular technology has also had a great impact in the treatment of pancreatic cancer, and several new 'designer drug' therapeutic strategies are being evaluated in clinical trials. The 'molecular age' has the promise of delivering still better results.

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Mesh compared with non-mesh methods of open groin hernia repair: systematic review of randomized controlled trials

EU Hernia Trialists Collaboration

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Background: Open tension-free methods of groin hernia repair have been widely adopted despite little rigorous evaluation.

Methods: Information was assimilated from all randomized or quasi-randomized trials comparing open mesh with open non-mesh methods to assess benefits and safety. Electronic databases were searched and members of the EU Hernia Trialists Collaboration consulted to identify trials. Prespecified data items were extracted from reports, and quantitative or, if not possible, qualitative meta-analysis was performed.

Results: Fifteen eligible trials, which included 4005 participants, were identified. There were similar numbers of complications in each group, with few data to address short-term pain and length of stay in hospital. Return to usual activities was quicker in the mesh group for seven of ten trials (*P* not significant). There were fewer reported recurrences in the mesh groups: overall 21 (1·4 per cent) of 1513 *versus* 72 (4·4 per cent) of 1634 (odds ratio 0·39 (95 per cent confidence interval 0·25–0·59); $P < 0{\cdot}001$).

Conclusion: Although the rigorous search maximized trial identification, formal meta-analysis was limited by the variation in trial reporting. Within the data available, mesh repair was associated with fewer recurrences.

Paper accepted 11 April 2000

British Journal of Surgery 2000, 87, 854–859

Introduction

Choice of repair method for inguinal hernia remains controversial. The most reliable evaluation should come from randomized controlled trials. The sample sizes of individual trials are usually modest, however, such that estimates of differences in outcome may be statistically imprecise. There may also be concerns about the generalizability of the findings because of variability in the standard methods of hernia repair and concerns that surgical skill and case-mix may differ.

Consideration of all similar randomized controlled trials together should overcome the problems of both imprecision and lack of generalizability. Precision is increased because the numbers of events, such as complications and recurrence, are larger. Generalizability is increased by consistent findings across a number of trials in varying settings. Recognition of the value of combining data from similar trials led in 1997 to the formation of the EU Hernia Trialists Collaboration, a group of surgical trialists who had participated in randomized trials of tension-free open and/or laparoscopic groin hernia repair[1]. This report is a systematic review of published data comparing open tension-free repair with traditional open sutured methods. The accompanying report, on pages 860–867 of this issue of the Journal, is a parallel comparison of laparoscopic with open methods of hernia repair.

Methods

Methods followed those of the Cochrane Collaboration[2]. Studies were eligible for inclusion if they were randomized or quasi-randomized trials comparing open mesh with open non-mesh groin hernia repair.

The electronic bibliographic databases MEDLINE and the Cochrane Central Controlled Trials Registry[2] were searched first. In MEDLINE, the first two stages of the standard Cochrane search strategy, described by Dickersin *et al.*[3] in 1994, were used with the appropriate specific search terms for open inguinal hernia repair. Further trials were sought from the reference lists of reports of known trials. Authors of identified randomized controlled trials were asked for information on any other trials known to them through the EU Hernia Trialists Collaboration. There was no language restriction.

As many as possible of a list of prespecified standard data items were extracted from eligible study reports. This was performed independently by two authors to minimize extraction errors. Where a difference of opinion existed, a third author arbitrated. The outcome measures sought were: operation conversions, duration of operation, postoperative and short-term pain, time to return to usual activities, complications (haematoma, seroma, infection, testicular injury and other serious complications), numbness and chronic pain after 3 months, and hernia recurrence.

The timing of outcome assessment varied between trials. For this reason, the variable 'postoperative pain' could include data collected on the second or third day, if no data were reported for the first postoperative day. Similarly, the variable 'short-term pain' could include information from days 7 to 10. Return to usual activities was defined as resumption of usual social activities or return to work. Some pain data had to be obtained by interpolation from graphs. Where relevant outcomes were reported only for separate mutually exclusive subgroups, a weighted average was calculated for means and a pooled standard deviation was derived from first principles.

The trials were grouped according to the types of operation being compared. Mesh operations were grouped as flat mesh, plug and mesh, or preperitoneal mesh. Non-mesh operations were grouped according to whether or not the Shouldice repair was the type of non-mesh operation used. The initial aim was to carry out formal quantitative meta-analyses of data from comparable trials using the methods described by Yusuf *et al.*[4] but, in the event, this was possible only for hernia recurrence. In four trials the denominators had to be estimated[5–8] and for one of these studies the numerators also had to be estimated from percentages[8]. In one trial[9] the denominators were hernias, not patients.

Where meta-analysis was not possible, a qualitative review was performed, looking for consistency between studies, principally in the direction of apparent effect and using the Sign test[10] when appropriate. In conducting Sign tests the exact binomial formula was used, and the conservative approach was adopted of comparing the number of trials favouring one management with all others, which included those where no difference in either direction was detected.

Results

The search identified 15 potentially eligible studies and all were included[5–9,11–20]. Twelve were reported in full papers and three as abstracts only. The trials included a total of 4005 randomized patients. The characteristics of the 15 trials are summarized in *Table 1*. The Lichtenstein technique was used as the method of mesh repair in ten trials, plug and mesh in two and preperitoneal mesh in one. Two reports specified only 'tension-free' repair. The Shouldice technique was the method of non-mesh repair in eight and another technique or a mixture of techniques was used in seven. All trials were restricted to elective inguinal hernia repair. Two included recurrent as well as primary hernias, ten were limited to primary hernias only, and these details were not reported for three.

The method of randomization used was stated explicitly for only four of the 15 trials: sealed envelopes in two, stratified randomization by computer in one, and the coin-toss method in one. In the other 11 trials the allocation was said to be 'randomized' but the exact method was not specified. The trials ranged in size from 64 to 672 randomized patients. The mean or median age ranged from 45 to 60 years, and the mean or median duration of follow-up ranged from 6 days to 5 years. In one trial the duration of follow-up was unclear.

The type of anaesthesia varied, with patients receiving general, regional or local anaesthetic, determined by the trial protocol or surgeon's choice. No conversions to another type of procedure were reported. The mean or median duration of operation was shorter in the mesh group in six trials, shorter in the non-mesh group in three trials, and was not reported or unclear for six studies ($P = 0{\cdot}51$, Sign test) (*Table 1*).

Postoperative complications were uncommon and of varying reported prevalence in the trials. The numbers of haematomas and infections were similar for mesh and non-mesh repairs. Although it was difficult to draw firm conclusions about seromas as they were often reported in combination with other complications, two studies reported a higher rate of seromas in the mesh group. Among the complications reported, none was judged potentially serious.

A minority of studies reported a measure of postoperative pain. On the first postoperative day, two of the three trials reporting pain on a visual analogue scale found less pain in the mesh group. At day 7 there was less pain in the mesh group for all three studies reporting this outcome.

Length of hospital stay was reported for six trials, with mean or median length of stay ranging from 1·1 to 6·7 days for the mesh groups and from 1·3 to 7·2 days for the non-mesh groups. Length of stay was reported as shorter in the mesh groups in five of the six trials ($P = 0{\cdot}22$, Sign test).

Time to return to usual activity was reported in ten studies (*Table 2*). Definitions varied widely, with five of the ten studies reporting return to work and the remainder reporting time to social activity or full recovery. Considering all reports of time to usual activity, patients in the mesh groups returned to the various activities more quickly than those in the non-mesh groups in seven trials, more slowly in two, and in a similar time in one ($P = 0{\cdot}34$, Sign test).

Table 1 Description of studies and duration of operations

Reference	Country	Project identification	Year	Duration of follow-up	No. randomized*	Duration of operation	
						Mesh	Non-mesh
Flat mesh *versus* Shouldice							
Barth *et al.*[11]	USA	New Hampshire 1998	1998	4 weeks	105	80 (70–96)†	95 (80–109)†
Castoro *et al.*[12]‡	Italy	Padova 1997	1996	3 weeks	383 (155)	—	—
Danielsson *et al.*[13]	Sweden	Halmstad 1999	1999	1 year	200 (178)	60(26)§	62(27)§
Koninger *et al.*[14]¶	Germany	Bietigheim 1998	1998	Median 18 months	280 (274)	48 (35–75)**	45 (35–60)**
Kux *et al.*[15]	Austria	Vienna 1994	1994	2·5 years	209	—	—
McGillicuddy[9]	USA	Lansing 1998	1998	Mean 5 (range 3–8) years	672	—	—
Schmitz *et al.*[16]	Germany	Bergisch-Gladbach 1997	1997	6 days	64	31(7·5)§	43(10)§
Flat mesh *versus* other non-mesh							
Friis and Lindahl[17]	Denmark	Copenhagen 1996	1996	2 years	234 (208)	—	—
Pappalardo *et al.*[18]	Italy	Rome 1995	1995	Mean 4·7 (range 3–6) years	100	56§	52§
Prior *et al.*[5]	UK	Pontypridd 1998	1998	Mean 7 (range 1–13) weeks	80	26·8 (12–49)**	27·5 (9–51)**
Vallribera *et al.*[6]‡,††	Spain	Barcelona 1997	1997	Unclear	425	—	—
van den Tol *et al.*[7]‡	The Netherlands	Rotterdam 1996	1996	Mean 13 months	300	Unclear	Unclear
Plug and mesh *versus* non-mesh							
Pirski *et al.*[19]	Poland	Gdansk 1997	1997	1–17 months	100	51·8(20·5)‡‡	63·8(29·8)‡‡
Zieren *et al.*[20]	Germany	Berlin 1998	1998	25(7) months§	240	36(14)§	47(17)§
Preperitoneal mesh *versus* non-mesh							
Johansson *et al.*[8]¶	Sweden	SCUR 1999	1999	1 year	613	38(14)§	37(16)§

*Values in parentheses are the numbers analysed; values are †median (interquartile range), §mean(s.d.) or mean alone, **mean (range); ‡‡meaning of values unclear; ‡reported as abstract only; ¶also included third (laparoscopic) arm; ††three-arm study (included one mesh and two non-mesh arms); SCUR, Scandinavian Clinics United Research

Chronic numbness and pain were reported for only a small minority of trials and with wide variation in the definitions used. There were few reported cases of chronic pain, with reported rates similar for the mesh and non-mesh groups. The only trial[9] reporting chronic numbness (paraesthesia) found fewer cases in the mesh group.

There was wide variability between the studies in both the hernia recurrence rates and the follow-up times reported. In five trials there were nine or more recurrences, in four three or fewer, and in four none in either group. Results tended to favour the mesh group, and overall there were 21 (1·4 per cent) of 1513 reported in the mesh groups compared with 72 (4·4 per cent) of 1634 in the non-mesh groups (odds ratio 0·39 (95 per cent confidence interval 0·25–0·59); $P < 0{\cdot}001$) (*Fig. 1*).

Discussion

The aim of this review and the accompanying one on laparoscopic repair (see pages 860–867) was to synthesize data from all rigorous trials, thereby increasing the applicability and usefulness of individual trials to policy and practice. Complete trial identification was maximized by using standard Cochrane review methods[2] supplemented by information on additional trials from the network of the EU Hernia Trialists Collaboration. The outcomes selected for the reviews were identified by a process of consultation with the collaborators[1] and were peer-reviewed by the Cochrane Collaboration. Therefore the methods used were rigorously defined before undertaking the review.

Firm conclusions could not be drawn for several of the prespecified outcomes because the data were not reported in an appropriate form for combining in a meta-analysis. For continuous outcomes the necessary means and standard deviations were not always reported (sometimes medians being reported correctly as the data were skewed). For dichotomous outcomes the relevant denominators were not always given explicitly. Not all the trials reported the prespecified outcomes and there was considerable variation in the definitions of outcomes used.

Table 2 Time to return to usual activity

Reference	Year	Definition of usual activity	Time to return to usual activity (days)	
			Mesh	Non-mesh
Open mesh *versus* Shouldice				
Barth *et al.*[11]	1998	Return to full activity	9*	9*
Castoro *et al.*[12]	1996	—		
Danielsson *et al.*[13]	1999	Return to work	18(8)†	24(13)†
Köninger *et al.*[14]	1998	Return to work	36 (14–97)‡	44 (14–120)‡
Kux *et al.*[15]	1994	Invalidity	26§	36§
McGillicuddy[9]	1998	—		
Schmitz *et al.*[16]	1997	—		
Open mesh *versus* other open non-mesh				
Friis and Lindahl[17]	1996	Return to work	23·6 (1–64)¶	18·6 (1–56)¶
Pappalardo *et al.*[18]	1995	Return to work	6§	17§
Prior *et al.*[5]	1998	Return to normal activity/work	25§	22§
Vallribera *et al.*[6]	1997	—		
van den Tol *et al.*[7]	1996	—		
Plug and mesh *versus* non-mesh				
Pirski *et al.*[19]	1997	Return to normal activity/work	14*	21*
Zieren *et al.*[20]	1998	Limitation of daily activities	4(2)†	11(4)†
Preperitoneal mesh *versus* non-mesh				
Johansson *et al.*[8]	1999	Return to full recovery	26§	36§

Values are *median, †mean(s.d.), §mean only, ¶median (range); ‡meaning of values unclear

Although an attempt was made to assess study quality, it was not possible to classify studies easily because of the lack of information regarding the method of randomization and other details. There was difficulty also in assessing whether analyses had followed the intention to treat principle. The recommendations in the CONsolidated Standards of Reporting Trials (CONSORT) statement[21] for presenting and reporting the results of randomized controlled trials are now widely adopted. The present task would have been easier and better accomplished if the trial reports considered in this review had followed these principles systematically. The authors strongly commend the CONSORT statement as a way of improving the quality of future reports of clinical trials.

Abdominal wall reinforcement using various types of mesh is increasingly popular in open inguinal hernia repair. Despite wide adoption, few rigorous evaluations have been carried out to compare these techniques with traditional suture techniques. Fifteen such trials were identified, involving over 4000 participants, all reported in the last 5 years. In the majority of these trials, the tension-free or Lichtenstein repair was the most frequently performed mesh technique, reflecting the most widely adopted open mesh operation. Three of the 15 studies were reported as abstracts only and so conveyed only limited information.

Because of the limitations described above, it was not possible either to identify clearly or to rule out putative benefits of mesh repair in respect of shorter operating time, less short-term pain and more rapid recovery. Nevertheless, it is possible to draw some conclusions based on the data available. Postoperative complications appear similar for both open groups, and there was no evidence that use of mesh increases the specific risks of deep infection and chronic pain. While the data on recurrence should be viewed cautiously because of variability of length of follow-up, method of ascertainment and reported prevalence, a consistent pattern did emerge of fewer recurrences reported in the mesh groups (*Fig. 1*).

The next step for the EU Hernia Trialists Collaboration is to collect individual patient data from the studies in this review. In other fields, particularly cancer, obtaining individual patient data has been accomplished successfully and meta-analyses of such data are considered the 'gold standard'[22]. As far as the authors are aware, such analyses have not previously been attempted in general surgery. The majority of trialists have agreed to contribute their data to this exercise. The results from the individual patient data analyses should allow much clearer identification of the potential benefits and disadvantages of mesh repair compared with traditional sutured methods in respect of all the outcomes considered in this review. In particular, it will be possible to carry out a more detailed evaluation of hernia recurrence over a longer follow-up period than is presently possible using only the results of published reports.

Acknowledgements

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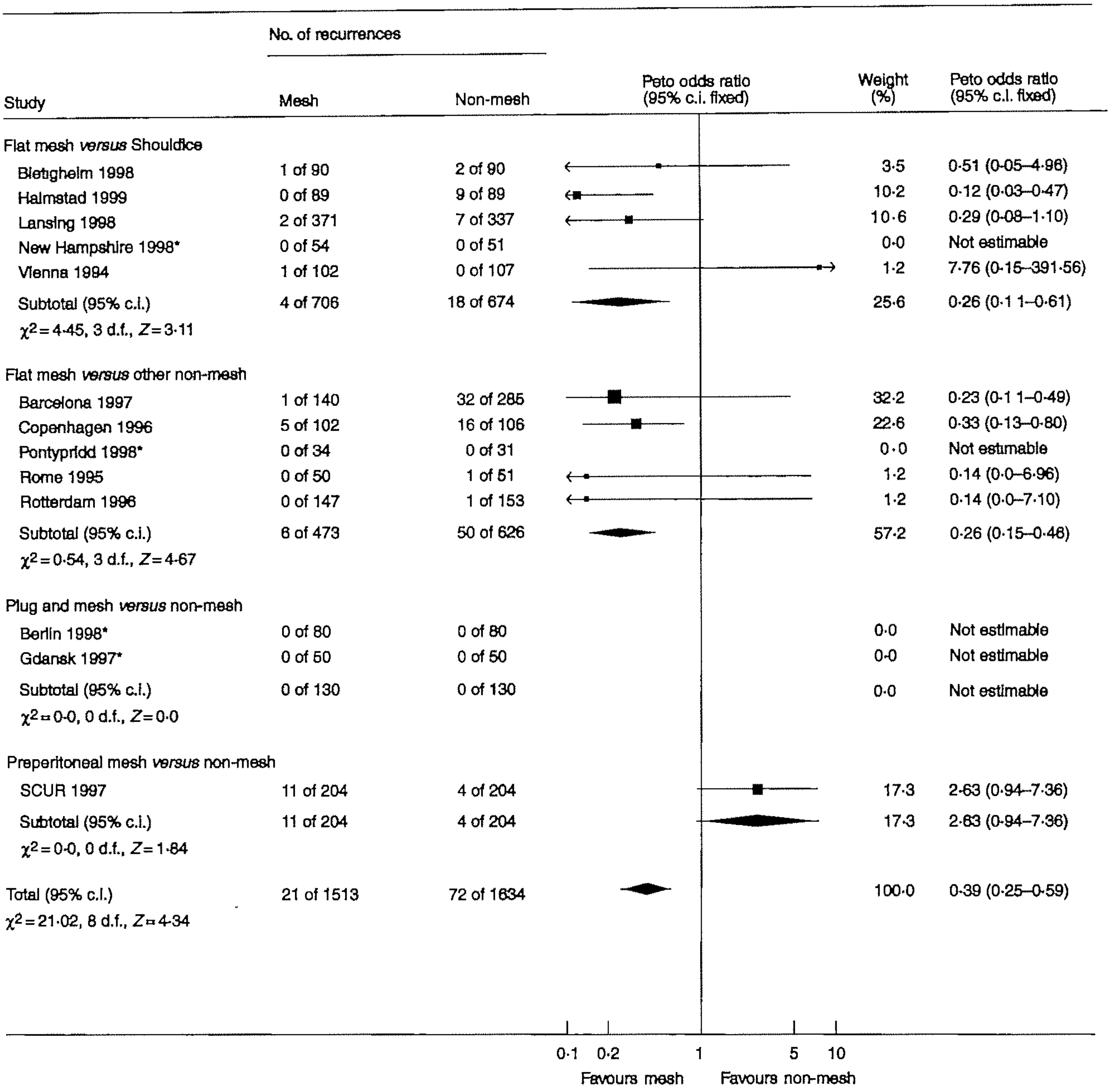

Study	No. of recurrences: Mesh	No. of recurrences: Non-mesh	Weight (%)	Peto odds ratio (95% c.i. fixed)
Flat mesh *versus* Shouldice				
Bietigheim 1998	1 of 90	2 of 90	3·5	0·51 (0·05–4·96)
Halmstad 1999	0 of 89	9 of 89	10·2	0·12 (0·03–0·47)
Lansing 1998	2 of 371	7 of 337	10·6	0·29 (0·08–1·10)
New Hampshire 1998*	0 of 54	0 of 51	0·0	Not estimable
Vienna 1994	1 of 102	0 of 107	1·2	7·76 (0·15–391·56)
Subtotal (95% c.i.) $\chi^2 = 4·45$, 3 d.f., $Z = 3·11$	4 of 706	18 of 674	25·6	0·26 (0·11–0·61)
Flat mesh *versus* other non-mesh				
Barcelona 1997	1 of 140	32 of 285	32·2	0·23 (0·11–0·49)
Copenhagen 1996	5 of 102	16 of 106	22·6	0·33 (0·13–0·80)
Pontypridd 1998*	0 of 34	0 of 31	0·0	Not estimable
Rome 1995	0 of 50	1 of 51	1·2	0·14 (0·0–6·96)
Rotterdam 1996	0 of 147	1 of 153	1·2	0·14 (0·0–7·10)
Subtotal (95% c.i.) $\chi^2 = 0·54$, 3 d.f., $Z = 4·67$	6 of 473	50 of 626	57·2	0·26 (0·15–0·46)
Plug and mesh *versus* non-mesh				
Berlin 1998*	0 of 80	0 of 80	0·0	Not estimable
Gdansk 1997*	0 of 50	0 of 50	0·0	Not estimable
Subtotal (95% c.i.) $\chi^2 = 0·0$, 0 d.f., $Z = 0·0$	0 of 130	0 of 130	0·0	Not estimable
Preperitoneal mesh *versus* non-mesh				
SCUR 1997	11 of 204	4 of 204	17·3	2·63 (0·94–7·36)
Subtotal (95% c.i.) $\chi^2 = 0·0$, 0 d.f., $Z = 1·84$	11 of 204	4 of 204	17·3	2·63 (0·94–7·36)
Total (95% c.i.) $\chi^2 = 21·02$, 8 d.f., $Z = 4·34$	21 of 1513	72 of 1634	100·0	0·39 (0·25–0·59)

Fig. 1 Hernia recurrence. *Denotes no recurrences in mesh or non-mesh group. c.i., Confidence interval; d.f., degrees of freedom; SCUR, Scandinavian Clinics United Research

(France), Andrew Kingsnorth (UK), Jesùs Merello (Spain), Paddy O'Dwyer (UK), John Payne (USA).

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(USA), B. Leibl (Germany), Ian Macintyre (UK), James McGillicuddy (USA), Guy Maddern (Australia), Bertrand Millat (France), Erik Nilsson (Sweden), Pär Nordin (Sweden), Alessandro Paganini (Italy), Giuseppe Pappalardo (Italy), Joan Sala Pedrós (Spain), R. Schmitz (Germany), Andreas Schwarz (Germany), Siegfried Shah (Germany), Robert Simmermacher (The Netherlands), Zbigniew Sledzinski (Poland), David Stoker (UK), Arthur Tanner (Ireland), Robert Taylor (UK), Jürgen Treckmann (Germany), Jerome Tschudi (Switzerland), Francesc Vallribera (Spain), Petrouska van den Tol (The Netherlands), Cees van Steensel (The Netherlands), Theo van Vroonhoven (The Netherlands), Wietske Vrijland (The Netherlands), James Wellwood (UK), Piotr Witkowski (Poland), Jürgen Zieren (Germany).

The EU Hernia Trialists Collaboration is supported by a grant from the EU BIOMED II work programme. The Health Services Research Unit is core funded by the Scottish Executive Health Department. The views expressed are those of the authors and not necessarily those of the funding bodies.

A more detailed review will be published and updated in the Cochrane Database of Systematic Reviews.[23]

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Laparoscopic compared with open methods of groin hernia repair: systematic review of randomized controlled trials

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Background: The place of laparoscopic groin hernia repair remains controversial. Individual randomized controlled trials alone have not provided statistically reliable results when considering recurrence, potentially serious complications and chronic pain.

Methods: A rigorous systematic review was performed of published data from all relevant randomized or quasi-randomized trials. Electronic databases were searched and members of the EU Hernia Trialists Collaboration consulted to identify trials. Prespecified data items were extracted from reports and, where possible, quantitative meta-analysis was performed.

Results: Thirty-four published reports of eligible trials were included, involving 6804 participants. Sample sizes ranged from 20 to 1051, with follow-up from 6 weeks to 36 months. Duration of operation was longer in the laparoscopic groups ($P < 0{\cdot}001$, Sign test). Operative complications were uncommon for both methods, but visceral and vascular injuries were more frequent in the laparoscopic group (4·7 per 1000 *versus* 1·1 per 1000). Postoperative pain was less among laparoscopic groups ($P = 0{\cdot}08$). Length of hospital stay did not differ significantly between groups ($P = 0{\cdot}50$), but return to usual activity was earlier for laparoscopic groups ($P < 0{\cdot}001$). Chronic pain and numbness were reported for only a small minority of trials. Overall, recurrences did not differ between groups, but comparison of laparoscopic with open non-mesh repair favoured laparoscopic methods, significantly so for transabdominal preperitoneal repair (Peto odds ratio 0·56 (95 per cent confidence interval 0·33–0·93); $P = 0{\cdot}026$).

Conclusion: Although the rigorous search maximized trial identification, variation in trial reporting made formal meta-analysis difficult. Laparoscopic repair was associated with less postoperative pain and more rapid return to normal activities, but it takes longer to perform and may increase the risk of rare, but serious, complications.

Paper accepted 11 April 2000

British Journal of Surgery 2000, 87, 860–867

Introduction

Minimal access, laparoscopic techniques appear to have short-term advantages over open techniques of inguinal hernia repair, but clinical concerns remain about hernia recurrence, safety and chronic pain. This systematic review of randomized or quasi-randomized controlled trials compared these methods with open methods in respect of their benefits and adverse events.

Methods

The methods used were similar to those described in the accompanying paper on pages 854–859 of this issue of the Journal comparing open mesh with open non-mesh methods of hernia repair[1]. They followed those of the Cochrane Collaboration[2]. Studies were eligible for inclusion if they were randomized or quasi-randomized trials comparing transabdominal preperitoneal (TAPP) or totally extraperitoneal (TEP) laparoscopic groin hernia repair with open groin hernia repair. The predefined set of outcomes was the same as in the accompanying paper, as were the definitions of outcome, except that, for the purposes of this review, a conversion was defined as a procedure initiated as laparoscopic but converted to open, or a procedure initiated as open but converted to laparoscopic.

Analysis

The trials were grouped according to the types of operation being compared: TAPP *versus* open mesh repair, TAPP *versus* open non-mesh repair, TEP *versus* open mesh, TEP

Table 1 Description of studies and length of operations

Reference	Country	Project identification	Year	Duration of follow-up	No. randomized*	Duration of operation	
						Laparoscopic	Open
TAPP *versus* mesh							
Aitola *et al.*[27]	Finland	Tampere 1998	1998	Median 18 months	60 (49)	72·5(15·8)†	61·5(16·0)†
Beets *et al.*[6]	The Netherlands	Maastricht 1999	1999	Mean 21 (range 6–36) months	79	79(32)†	56(16)†
Filipi *et al.*[28]	USA	Omaha 1996	1996	Mean 11 (range 1–24) months	53	109‡	87‡
Heikkinen *et al.*[17]	Finland	Kokkola 1997	1997	Median 10 months	38	71·5 (43–140)§	45·0 (16–83)§
Johansson *et al.*[16]¶	Sweden	SCUR 1999	1999	1 year	613	65(25)†	38(14)†
Köninger *et al.*[29]¶	Germany	Bietigheim 1998	1998	Median 18 months	280 (274)	52 (25–80)‡	48 (35–75)‡
Paganini *et al.*[30]	Italy	Ancona 1998	1998	Mean 28 (i.q.r. 24·9–30·9) months	108	72·9(27·6)†	55·6(31·9)†
Payne *et al.*[19]	USA	Hawaii 1994	1994	Median 10 (range 7–18) months	100	76·0**	59·9**
Sarli *et al.*[31]	Italy	Parma 1997	1997	Mean 36 (range 18–54) months	108	76·9 (45–160)††	69·7 (37–135)††
Wellwood *et al.*[10]	UK	Whipps Cross 1998	1998	3 months	403 (400)	—	—
Zieren *et al.*[26]¶	Germany	Berlin 1998	1998	Mean(s.d.) 25(7) months	240	61(12)†	36(14)†
TAPP *versus* non-mesh							
Damamme *et al.*[32]	France	Caen 1998	1998	Mean 15·3 (range 4–30) months	64 (55)	89**	56**
Dirksen *et al.*[13]	The Netherlands	Maastricht 1998	1998	Mean 24 (range 15–36) months	210 (175)	90·0(32·8)†	45·6(15·7)†
Hauters *et al.*[14]	Belgium	Tournai 1996	1996	Median 30 (range 19–42) months	70	68(24)‡	63(14)‡
Johansson *et al.*[16]¶	Sweden	SCUR 1999	1999	1 year	613	65(25)†	37(16)†
Juul and Christensen[18]	Denmark	Nyborg 1999	1999	Lap: median 12 (range 8–17) months Open: median 12 (range 8–23) months	287 (268)	77 (30–200)§	45 (20–80)§
Kald *et al.*[33]	Sweden	Huddinge 1997	1997	2 months (199); 1 year (194)	200 (199)	72(30)†	62(25)†
Köninger *et al.*[29]¶	Germany	Bietigheim 1998	1998	Median 18 months	280 (274)	52 (25–80)‡	45 (35–60)‡
Kozol *et al.*[7]	USA	Michigan 1997	1997	Unclear (at least 2 days)	62	128(38)†	126(37)†
Kunz *et al.*[8]	Germany	Ulm 1993	1993	Unclear	20	—	—
Lawrence *et al.*[34]	UK	Oxford 1995	1995	6 weeks	130 (124)	72(11)†	32(8)†
Leibl *et al.*[35]	Germany	Stuttgart 1995	1995	Median 16 (range 13–21) months	102	65 (30–135)‡	47.5 (30–110)‡
Maddern *et al.*[36]	Australia	Adelaide 1994	1994	Median 243 (range 160–436) days	86	35 (20–55)§	30.5 (15–70)§
Schrenk *et al.*[25]¶	Austria	Linz 1996	1996	3 months	86	46·0(9·2)†	38·4(9·7)†
Stoker *et al.*[12]	UK	Whipps Cross 1994	1994	Mean 7 months	150	Unclear	Unclear
Tanphiphat *et al.*[37]	Thailand	Bangkok 1998	1998	Mean 32 (range 12–52) months	120	95(28)†	67(27)†
Tschudi *et al.*[38]	Switzerland	Aarberg 1996	1996	Mean 201 days	87	95 (45–240)††	64 (30–105)††
Zieren *et al.*[26]¶	Germany	Berlin 1998	1998	Mean(s.d.) 25(7) months	240	61(12)†	47(17)†
TEP *versus* mesh							
Champault *et al.*[21]	France	Paris 1997	1997	Lap: mean 610 days Open: mean 610 days (range 30–1600) days	100	80·6(31·3)†	70·3(15·7)†
Khoury[39]	Canada	Quebec 1998	1998	Median 17 (range 2–38) months	292	31·5 (5–80)§	30·5 (10–70)§
Merello *et al.*[9]	Spain	Madrid 1997	1997	'Short'	120	—	—
Payne *et al.*[22]	USA	Hawaii 1996	1996	Median 20 (range 4–40) months	100	Unclear	Unclear
TEP *versus* non-mesh							
Champault *et al.*[20]	France	Paris 1994	1994	Mean 12·3 (range 2–21) months	181	69·3**	62·3**
Liem *et al.*[24]	The Netherlands	Coala Trial Group 1997	1997	Median 607 (i.q.r. 369–731) days	1051	45 (35–60)‡‡	40 (30–45)‡‡
Nathanson *et al.*[23]	Australia	Brisbane 1996	1996	Median 24 months	184	—	—
Schrenk *et al.*[25]¶	Austria	Linz 1996	1996	3 months	86	52·3(13·9)†	38·4(9·7)†
Mixed laparoscopic *versus* mixed open							
Barkun *et al.*[40]	Canada	Montreal 1995	1995	Median 14 months	92	86·7(30·2)†	79·8(58·7)†
MRC Trial Group[11]	UK	MRC multicentre 1999	1999	1 year	928	58·4(22·6)†	43·4(15·9)†

*Values in parentheses are the numbers analysed; values are †mean(s.d.), §median (range), **mean, ††mean (range), ‡‡median (i.q.r.); ‡meaning of values unclear; ¶three-armed trial (entered twice in table in appropriate comparisons). TAPP, transabdominal preperitoneal; TEP, totally extraperitoneal; Lap, laparoscopic; MRC, Medical Research Council; SCUR, Scandinavian Clinics United Research; i.q.r., interquartile range

versus open non-mesh, and mixed laparoscopic *versus* mixed open. The initial aim was to carry out formal quantitative meta-analyses of data from comparable trials using the methods described by Yusuf and colleagues[3]. In the event, there were difficulties in doing this with all prespecified outcomes. Some data were not presented in a form sufficiently similar to allow quantitative synthesis; in these cases a qualitative review was performed seeking consistency between studies, principally in the direction of apparent effect, using the Sign test[4]. The conservative approach was adopted of comparing the number of trials favouring laparoscopic management with all others, which included those in which no differences in either direction were detected. Other data items sought were available in the reports of only a minority of trials. For some outcomes there were difficulties combining data because of apparently varying definitions and variable follow-up.

Results

The search identified 35 potentially eligible studies. One trial was excluded because of major deviation from intention to treat analysis[5]. Of the 34 trials included[6–40], 30 were reported in full papers and four only as abstracts. The trials included analysis of 6804 randomized patients. The characteristics of the 34 trials are summarized in *Table 1*.

All trials included patients who were eligible for elective inguinal hernia repair. Seventeen included both recurrent and primary hernias, 12 primary hernias only, one recurrent hernias only[6], and for four the type of hernia was not reported. The common exclusion criteria were: unfit for surgery or general anaesthesia, incarcerated or strangulated hernia, inguinoscrotal hernia, previous lower abdominal surgery, and pregnancy.

Where specified, the most common method of randomization was by sealed envelopes (12 trials), random number tables (although exact details were not described) (three), a central randomization service (four), computer-generated random numbers (three) and random selection by cards (one). In 11 trials, the allocation was said to be randomized but the method was not specified. The trials ranged in size from 20 to 1051 randomized patients. The mean or median age ranged from 38·7 to 67·5 years. The mean or median duration of follow-up ranged from 6 weeks to 36 months. In three trials the duration of follow-up was unclear[7–9].

Operative details also varied. Across the trials, where reported, all but seven of the patients allocated to laparoscopic repair received a general anaesthetic; of the remaining seven, one had local and six had regional anaesthesia. Patients in the open groups received general, regional or local anaesthesia, determined by the trial protocol or surgeon's choice. In total, 53 laparoscopic operations were stated to have been converted to an open procedure and one open procedure was converted to a laparoscopic repair owing to the presence of a mesh[10]. The mean or median duration of operation was longer in the laparoscopic group in all 28 trials for which the information was available ($P < 0.001$, Sign test) (*Table 1*).

Postoperative complications were uncommon and of varying reported prevalence in the trials. Overall, there appeared to be fewer haematomas in the laparoscopic groups, but this difference disappeared when data from the relatively large UK Medical Research Council multicentre trial[11] were excluded. Where reported, infection and testicular injury also appeared to be less frequent in the laparoscopic groups, but these results were largely dependent on the 1994 Whipps Cross trial[12]. All trials that reported data, except one[11], had more cases of seroma in the laparoscopic groups. Eighteen trial reports mentioned other complications. Overall, there were 15 potentially serious visceral or vascular injuries in the laparoscopic groups compared with four in the open groups (4·7 *versus* 1·1 per 1000) (*Table 2*). Across the trials there were eight reports of reoperation in the laparoscopic groups compared with 12 in the open groups (two in the second open group in a three-group trial[29]).

Table 2 Potentially serious complications

Complication	Laparoscopic repair	Open repair
Intraoperative		
Visceral		
Bladder injury[11,16,27]	4	0
Puncture of stomach[13]	1	0
Small bowel injury[11]	0	1
Vascular		
Epigastric bleeding[26]	2	0
Trocar injury to left common iliac artery[11]	1	0
Postoperative		
Visceral		
Small bowel obstruction[11,38]	2	0
Vascular		
Bleeding/haematoma[12,13,20,36,38]	5	3

Of the 16 trial reports that included a measure of postoperative pain, 12 favoured the laparoscopic group ($P = 0.08$, Sign test). At 7–10 days after operation, a measure of pain was reported for ten trials, of which seven favoured the laparoscopic group ($P = 0.34$, Sign test). Length of hospital stay was reported for 20 trials with mean or median length of stay ranging from 225 min to 4·9 days for the laparoscopic groups and from 134 min to 7·3 days for the open groups. Length of stay was shorter for the laparoscopic groups in 12 trials, longer in six trials and similar for two ($P = 0.50$, Sign test).

Definitions of 'time to return to usual activity' varied widely (*Table 3*), with return to work being the most commonly mentioned (18 trials). Considering all reports of time to usual activity, the laparoscopic groups returned to the various activities more quickly than the open groups in 24 trials, more slowly in two, in a similar time in one, and the information was not available for seven trials ($P < 0.001$, Sign test) (*Table 3*).

Table 3 Time to return to usual activity

Reference	Year	Definition of usual activity	Time to return to usual activity (days) Laparoscopic	Open
TAPP *versus* mesh				
Aitola *et al.*[27]	1998	Return to work or normal activity	7 (1–60)*	5 (1–30)*
Beets *et al.*[6]	1999	Return to work	13(8·2)†	23(12·4)†
Filipi *et al.*[28]	1996	—	—	—
Heikkinen *et al.*[17]	1997	Return to work	14 (8–26)*	19 (6–40)*
Johansson *et al.*[16]‡	1999	Sick leave	14·7†	17·7†
Koninger *et al.*[29]‡	1998	Return to work	25 (6–120)§	36 (14–97)§
Paganini *et al.*[30]	1998	Return to work	15 (10–25)¶	14 (7–30)¶
Payne *et al.*[19]	1994	—	—	—
Sarli *et al.*[31]	1997	Return to normal activity	14†	14†
Wellwood *et al.*[10]	1998	Return to usual activity	Stratified data	Stratified data§§
Zieren *et al.*[26]‡	1998	Limitation of daily activities	3(2)†	4(2)†
TAPP *versus* non-mesh				
Damamme *et al.*[32]	1998	Return to work	28·6†	35·5†
Dirksen *et al.*[13]	1998	Return to work	Stratified data	Stratified data§§
Hauters *et al.*[14]	1996	Return to work	29(11)§	30(12)§
Johansson *et al.*[16]‡	1999	Sick leave	14·7†	17·9†
Juul and Christensen[18]	1999	Return to normal activities	13 (1–56)*	18 (3–55)*
Kald *et al.*[33]	1997	Return to work	Stratified data	Stratified data§§
Köninger *et al.*[29]‡	1998	Return to work	25 (6–120)**	44 (14–120)**
Kozol *et al.*[7]	1997	—	—	—
Kunz *et al.*[8]	1993	—	—	—
Lawrence *et al.*[34]	1995	Return to work or normal activity	22 (2–99)*	28 (1–103)*
Leibl *et al.*[35]	1995	Return to work	21**	38**
Maddern *et al.*[36]	1994	Return to work	17·5 (5–73)*	30 (7–78)*
Schrenk *et al.*[25]‡	1996	Time off work	4·9(0·7)§	4·8(0·6)§
Stoker *et al.*[12]	1994	Return to work	14††	28††
Tanphiphat *et al.*[37]	1998	Return to work	14 (8–25)¶	15 (11–21)¶
Tschudi *et al.*[38]	1996	—	—	—
Zieren *et al.*[26]‡	1998	Limitation of daily activities	3(2)†	11(4)†
TEP *versus* mesh				
Champault *et al.*[21]	1997	Return to work	17(11)†	35(14)†
Khoury[39]	1998	Return to work	8 (5–13)*	15(11–21)*
Merello *et al.*[9]	1997	Return to work	11†	26†
Payne *et al.*[22]	1996	—	—	—
TEP *versus* non-mesh				
Champault *et al.*[20]	1994	—	—	—
Liem *et al.*[24]	1997	Return to work	14 (7–21)¶	21 (12–33)¶
Nathanson *et al.*[23]	1996	Return to normal activity	10**	21**
Schrenk *et al.*[25]‡	1996	Time off work	4·6(0·6)§	4·8(0·6)§
Mixed laparoscopic *versus* mixed open				
Barkun *et al.*[40]	1995	Convalescence	9·6(7·6)†	10·9(7·4)†
MRC Trial Group[11]	1999	Return to usual activity	Stratified data	Stratified data§§

Values are *median (range), †mean(s.d.) or mean only, §mean(s.e.m.), ¶median (interquartile range), ††median; **meaning of values unclear; ‡three-armed trial (entered twice in table in appropriate comparisons); §§in all strata shorter time in laparoscopic groups. TAPP, transabdominal preperitoneal; TEP, totally extraperitoneal; MRC, Medical Research Council

Overall, 65 recurrences (2·3 per cent) were reported among 2845 patients allocated to laparoscopic repair and 93 (2·9 per cent) among 3197 allocated to open repair. *Fig. 1* is a meta-analysis of these data subdivided into the main comparisons. In respect of the comparisons of TAPP and TEP *versus* open mesh repairs, there were non-significant higher rates of recurrence in the laparoscopic groups. The comparisons of TAPP *versus* open non-mesh repair favoured TAPP with 23 recurrences in 1107 patients compared with 39 in 1080 (Peto odds ratio 0·56 (95 per cent confidence interval 0·33–0·93); $P = 0{\cdot}026$). The estimated effect was similar in the TEP *versus* open non-mesh comparison, but was not statistically significant.

Chronic numbness was described in only three trials[6,13,14] and appeared to be less common among those having laparoscopic surgery (one *versus* ten). In one trial[15]

Study	No. of recurrences Laparoscopic	Open	Peto odds ratio (95% c.i. fixed)
TAPP *versus* mesh			
Ancona 1998	2 of 52	0 of 56	8·14 (0·50–132·07)
Berlin 1998*	0 of 80	0 of 80	Not estimable
Bietigheim 1998*	1 of 94	1 of 90	0·96 (0·06–15.43)
Hawaii 1994*	0 of 48	0 of 52	Not estimable
Kokkola 1997*	0 of 20	0 of 18	Not estimable
Maastricht 1998	6 of 42	1 of 37	4·12 (0·88–19·32)
Omaha 1996	0 of 24	2 of 29	0·16 (0·01–2·58)
SCUR 1999*	4 of 205	11 of 204	0·38 (0·14–1·06)
Tampere 1998	3 of 24	2 of 25	1·62 (0·26–10·10)
Whipps Cross 1998*	0 of 200	0 of 200	Not estimable
Subtotal (95% c.i.)	16 of 789	17 of 791	0·93 (0·46–1·87)
χ^2 = 10·73, 5 d.f., Z = 0·21			
TAPP *versus* non-mesh			
Aarberg 1996	1 of 44	2 of 43	0·49 (0·05–4·87)
Adelaide 1994	2 of 42	0 of 44	7·94 (0·49–129·16)
Bangkok 1998	1 of 58	0 of 57	7·26 (0·14–366·10)
Berlin 1998*	0 of 80	0 of 80	Not estimable
Bietigheim 1998*	1 of 94	2 of 90	0·49 (0·05–4·75)
Huddinge 1997	0 of 110	3 of 89	0·10 (0·01–1·03)
Linz 1996	1 of 28	0 of 34	9·15 (0·18–470·02)
Maastricht 1998	7 of 88	22 of 87	0·29 (0·13–0·64)
Nyborg 1999	4 of 138	3 of 130	1·26 (0·28–5·64)
Oxford 1995	1 of 58	0 of 66	8·48 (0·17–431·00)
SCUR 1999*	4 of 205	4 of 204	1·00 (0·25–4·03)
Stuttgart 1995*	0 of 53	0 of 48	Not estimable
Tournai 1996	1 of 34	3 of 33	0·34 (0·05–2·53)
Whipps Cross 1994*	0 of 75	0 of 75	Not estimable
Subtotal (95% c.i)	23 of 1107	39 of 1080	0·56 (0·33–0·93)
χ^2 = 15·70, 10 d.f., Z = 2·22			
TEP *versus* mesh			
Hawaii 1996	1 of 50	0 of 50	7·39 (0·15–372·41)
Madrid 1997	0 of 60	0 of 60	Not estimable
Paris 1997	3 of 51	1 of 49	2·69 (0·37–19·71)
Quebec 1998	3 of 150	4 of 142	0·71 (0·16–3·16)
Subtotal (95% c.i.)	7 of 311	5 of 353	1·34 (0·43–4·22)
χ^2 = 1·90, 2 d.f., Z = 0·50			
TEP *versus* non-mesh			
Coala Trial Group 1997	17 of 487	31 of 507	0·57 (0·32–1·01)
Linz 1996*	0 of 24	0 of 34	Not estimable
Paris 1994*	0 of 89	0 of 92	Not estimable
Subtotal (95% c.i.)	17 of 600	31 of 633	0·57 (0·32–1·01)
χ^2 = 0·0, 0 d.f., Z = 1·93			
Miscellaneous laparoscopic *versus* open			
Montreal 1995	0 of 43	1 of 49	0·15 (0·00–7·77)
MRC multicentre 1999	7 of 362	0 of 349	7·25 (1·64–32·10)
Subtotal (95% c.i.)	7 of 405	1 of 398	4·47 (1·11–17·96)
χ^2 = 3·24, 1 d.f., Z = 2·11			
All laparoscopic *versus* all open			
Total (95% c.i.)	65 of 2845	93 of 3197	0·76 (0·55–1·05)
χ^2 = 43·40, 21 d.f., Z = 1·55			

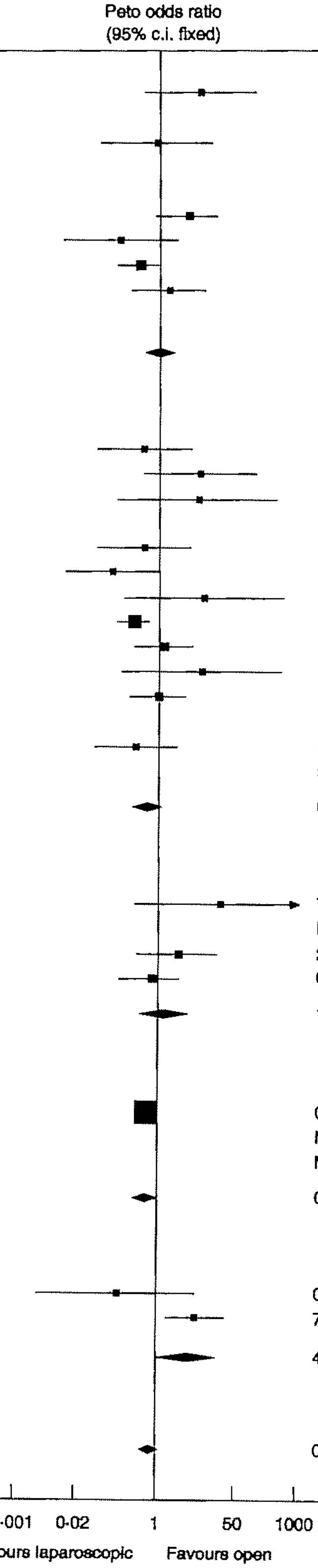

Fig. 1 Hernia recurrence. *Denotes no recurrences in either laparoscopic or open group. TAPP, transabdominal preperitoneal; TEP, totally extraperitoneal; MRC, Medical Research Council; c.i., confidence interval; d.f., degrees of freedom; SCUR, Scandinavian Clinics United Research

numbness within 3 months was reported and again appeared less often in the laparoscopic group, three of 200 patients being affected compared with 37 of 200. Three trials[6,13,16] reported chronic pain, with 24 of 335 patients affected in laparoscopic groups *versus* 15 of 532 in open groups. A further three trials[17–19] reported pain of more than 1 month's duration; ten of 206 patients were affected in laparoscopic groups and 17 of 200 in open groups.

Discussion

This systematic review successfully identified usable published reports of 34 eligible trials comparing laparoscopic groin hernia repair with open repair. A similar review by Chung and Rowland[41] identified only 18 trials because their search strategy was limited to MEDLINE. Of the 18 trials identified, they reported that only 14 had usable statistical data, even after contacting the trialists for clarification of results. They chose to combine only data on length of operation, pain, time to recovery and hernia recurrence, and did not address complications.

Despite the rigorous design of the present systematic review, meta-analysis of the results relating to the predefined outcomes was difficult. Means and standard deviations were not always reported for continuous outcomes (sometimes medians were correctly reported because the data were skewed). Data describing the prespecified outcomes required for meta-analysis were not always reported; for example, only two trials reported chronic pain, three reported chronic numbness, and definitions of 'return to usual activity' varied widely. Appropriate denominators for the groups were not always given and the length of follow-up was variable. In addition, both the likely overlap between some trials[20,21] and pooling of data from others[22] complicated data abstraction. Analysis of some trials was not based on intention to treat. Those reported as abstracts had only very limited details[8,9,22,23] and in five trials postoperative pain was estimated from a graph[12,17,24–26]. Thus the methods of trial reporting made formal meta-analysis difficult and potentially biased.

In spite of these difficulties it was possible to confirm that return to usual activity was faster following laparoscopic repair. However, operating times were longer and there appears to be a higher serious complication rate in respect of visceral (especially bladder) and vascular injuries. All the potentially serious intraoperative complications in these groups followed TAPP repair.

The findings relating to recurrence are consistent with those in the accompanying review[1], which shows fewer associated with open mesh repair. Both of the subgroup comparisons of laparoscopic methods (which use mesh) with non-mesh open methods appear to favour the laparoscopic method, although this was not statistically significant for the TEP *versus* non-mesh comparison. However, the results for each of these comparisons are highly dependent on the results of a single trial[13,24]. The comparisons of laparoscopic methods *versus* open mesh methods do not demonstrate a clear difference. However, if the UK Medical Research Council trial, comparing a predominantly TEP policy with a predominantly open mesh policy, is included in the TEP *versus* open mesh comparison, the results favour open mesh.

Despite the clear findings of this review in respect of short-term outcomes, the authors believe that analysis of individual patient data from trials is now necessary to make formal quantitative meta-analysis possible. This should also allow the inclusion of longer-term follow-up data and will be the next step for the EU Hernia Trialists Collaboration. Most of the principal investigators of the trials considered here have agreed to contribute to this exercise. This will permit the observed short-term differences to be quantified reliably and, more importantly, will allow possible differential effects on rarer, longer-term outcomes (chronic pain, numbness and recurrence) to be considered more rigorously. The aim is to produce clear recommendations for the surgical management of inguinal hernia.

Acknowledgements

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Guy Maddern (Australia), Bertrand Millat (France), Erik Nilsson (Sweden), Pär Nordin (Sweden), Alessandro Paganini (Italy), Giuseppe Pappalardo (Italy), Joan Sala Pedrós (Spain), R. Schmitz (Germany), Andreas Schwarz (Germany), Siegfried Shah (Germany), Robert Simmermacher (The Netherlands), Zbigniew Sledzinski (Poland), David Stoker (UK), Arthur Tanner (Ireland), Robert Taylor (UK), Jürgen Treckmann (Germany), Jerome Tschudi (Switzerland), Francesc Vallribera (Spain), Petrouska van den Tol (The Netherlands), Cees van Steensel (The Netherlands), Theo van Vroonhoven (The Netherlands), Wietske Vrijland (The Netherlands), James Wellwood (UK), Piotr Witkowski (Poland), Jürgen Zieren (Germany).

The EU Hernia Trialists Collaboration is supported by a grant from the EU BIOMED II work programme. The Health Services Research Unit is core funded by the Scottish Executive Health Department. The views expressed are those of the authors and not necessarily those of the funding bodies.

A more detailed review will be published and updated in the Cochrane Database of Systematic Reviews.[42]

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Randomized clinical trial of micronized flavonoids in the early control of bleeding from acute internal haemorrhoids

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Background: Patients with acute bleeding from internal haemorrhoids often have to be referred by the general practitioner to the surgeon for definitive treatment with invasive outpatient procedures. At the initial consultation, patients frequently seek postponement of immediate surgery to a more convenient time. Effective and rapid non-invasive control of acute bleeding could be of practical use in scheduling surgery to a time convenient to both patient and surgeon.

Methods: In a 90-day randomized, double-blind study treatment with a micronized purified flavonoid fraction (MPFF) was compared with placebo, in 100 outpatients who presented for treatment of acute internal haemorrhoids of less than 3 days' duration. The primary endpoint was cessation of bleeding on the third day of treatment.

Results: Of 50 patients randomized to each group, acute bleeding ceased by the third day in 40 (80 per cent) who received MPFF compared with 19 (38 per cent) who had placebo ($P < 0{\cdot}01$). Mean(s.d.) duration of acute bleeding from onset to cessation of 4·9(1·6) days was 2·1 (95 per cent confidence interval 1·2–2·9) days less than that in patients receiving placebo ($P < 0{\cdot}01$). Continued treatment in patients with no bleeding prevented a relapse in 30 of 47 patients, compared with 12 of 30 receiving placebo ($P < 0{\cdot}05$).

Conclusion: Patients with acute internal haemorrhoids treated with MPFF had rapid cessation of bleeding and a reduced risk of relapse. This could be of value in the more convenient timing of treatment with invasive outpatient procedures.

Paper accepted 19 January 2000

British Journal of Surgery 2000, 87, 868–872

Introduction

Patients with acute internal haemorrhoids are frequently treated successfully with invasive outpatient procedures, such as rubber-band ligation, injection sclerotherapy, infrared photocoagulation or cryosurgery[1]. However, in spite of careful technique, many patients experience pain and discomfort. For example, with ligation up to 80 per cent have pain in the first 24 h, 60 per cent in the next 24 h and 28 per cent are unable to resume normal activity on the day of treatment[2]. When informed of this inconvenience at the initial consultation, patients will frequently seek postponement of immediate surgery to a more convenient time. Furthermore, although simple, these outpatient invasive procedures require skill and practice, and patients usually have to be referred by the general practitioner to an experienced surgeon which again involves a delay. There is therefore a practical need for effective and rapid non-invasive control of bleeding which will allow immediate definitive surgery to be deferred to a time more convenient to patient and surgeon.

One of the pathogenic processes implicated in the acute bleeding of internal haemorrhoids is stagnation and stasis of blood in the vascular plexuses of the prolapsed anal cushions[3]. It has been demonstrated that stasis activates white cells to release inflammatory mediators and cause an inflammatory response which results in increased permeability, fragility and necrosis of the vessel wall[3]. The anal cushions are therefore easily injured by the passage of stool and bleed. The flavonoid compounds that are frequently prescribed for acute haemorrhoids in several Asian and European countries may suppress bleeding by a mechanism which increases venous tone, reduces stasis, inhibits inflammatory mediators and enhances lymphatic drainage[4]. A micronized purified flavonoid fraction (MPFF), of 90 per cent diosmin and 10 per cent hesperidin (Daflon 500; Les Laboratoires Servier, France), has been shown to reduce the severity of bleeding[5] and prevent its relapse[6] in comparison to placebo. However, its effectiveness and speed in stopping the bleeding altogether, to be of practical use in delaying invasive treatment, has not been demonstrated. This double-blind, randomized, placebo-controlled study examined whether MPFF is effective in rapidly stopping the bleeding of internal haemorrhoids and preventing a relapse.

Patients and methods

Patients

The institutional ethics committee approved the study protocol. Patients were recruited from the surgical outpatient clinic of a tertiary care teaching hospital where both new and referred patients are eligible for treatment. Consecutive outpatients of either sex, over 18 years of age, with a past history of haemorrhoids of less than 18 months, and presenting with acute rectal bleeding of less than 3 days in association with visibly distended or displaced anal cushions conforming to grade 1 or 2 internal haemorrhoids[1] were identified on proctoscopic examination. Of these, patients were eligible for the study if there was no anal fissure, inflammatory bowel disease, colorectal cancer or pregnancy; previous laser treatment or use of a flavonoid drug 1 month before inclusion; and if they were not being treated with analgesics, topical antihaemorrhoidal ointments, non-steroidal anti-inflammatory drugs, steroids, anticoagulants or antiplatelet agents.

Study design, assessments and treatments

After giving written informed consent, eligible patients were assessed at baseline (*Table 1*) for demographic characteristics; vegetarian or non-vegetarian diet; self-assessed duration and severity of bleeding (mild, moderate, or severe); degree of haemorrhoids (grade 1, only bleeding with no prolapse; grade 2, bleeding and prolapse which reduced spontaneously); associated disease; blood pressure; and serum levels of creatinine, aspartate aminotransferase, alanine aminotransferase and bilirubin. They were then randomized to receive MPFF or placebo under double-blind conditions (*Fig. 1*). Treatment was given in two sequential phases. In the first phase of 7 days to assess impact on bleeding (acute treatment), patients took six tablets per day for 4 days and four per day for 3 days. In the second phase (prevention of relapse), patients whose bleeding had stopped by the end of the first phase took two tablets per day for 83 days. Daily medication was in divided doses after lunch and dinner. Tablets containing micronized diosmin 450 mg and hesperidin 50 mg or placebo (Serdia Pharmaceuticals (India), Bombay, India) were identical in appearance. Patients were advised to continue their usual diet, but avoid any local or systemic treatment for haemorrhoids during the study.

After 7 days of acute treatment, patients were reassessed on the eighth day with a proctoscopic examination, and a history was obtained of the treatment day on which bleeding had stopped. Patients with continuing bleeding were withdrawn and treated by other means. The remaining patients entered the second phase (prevention of relapse) and were examined on the 15th, 30th, 60th and 90th day of the study for relapse of bleeding. Side-effects were monitored by asking open-ended questions to identify any problems since the previous visit, and a tablet count was taken to assess compliance with medication. In the event of relapse, patients were withdrawn and offered treatment by

Table 1 Baseline characteristics at inclusion

Characteristic	Placebo (*n*=50)	MPFF (*n*=50)
Age (years)*	33·3(11·1)	34·8(12·7)
Sex†		
Men	41 (82)	38 (76)
Women	9 (18)	12 (24)
Vegetarian	22 (44)	27 (54)
History of haemorrhoids		
Total duration (months)*	10·8(6·2)	9·9(14·3)
Duration of acute bleeding†		
1 day	5 (10)	6 (12)
2 days	27 (54)	21 (42)
3 days	18 (36)	23 (46)
Severity of bleeding†		
Mild	34 (68)	37 (74)
Moderate	15 (30)	12 (24)
Severe	1 (2)	1 (2)
Previous treatment†		
Sclerotherapy	2 (4)	0 (0)
Local analgesic ointment	8 (16)	4 (8)
Homoeopathic	8 (16)	7 (14)
Haemorrhoid grade†‡		
Grade 1	36 (72)	34 (68)
Grade 2	14 (28)	16 (32)
Thrombosis†	0 (0)	1 (2)
Associated disease†§	5 (10)	4 (8)
Blood pressure (mmHg)*		
Systolic	117·6(12·6)	116·9(10·2)
Diastolic	76·2(7·9)	77·3(7·9)
Serum creatinine (mg/dl)*	0·9(0·2)	0·9(0·3)
Serum AST (units/l)*	43·4(18·7)	36·1(14·4)
Serum ALT (units/l)*	42·3(30·2)	40·5(23·2)
Serum bilirubin (mg/dl)*	0·7(0·2)	0·7(0·2)

*Values are mean(s.d.); †values in parentheses are percentages. ‡Grade 1, bleeding only with no prolapse; grade 2, prolapse which reduced spontaneously. §One patient each with hepatitis, hypothyroidism and coronary artery disease, and two patients with hypertension in the placebo group; one patient each with prostatic hypertrophy and bronchial asthma, and two patients with hypertension in the micronized purified flavonoid fraction (MPFF) group. AST, aspartate aminotransferase; ALT, alanine aminotransferase

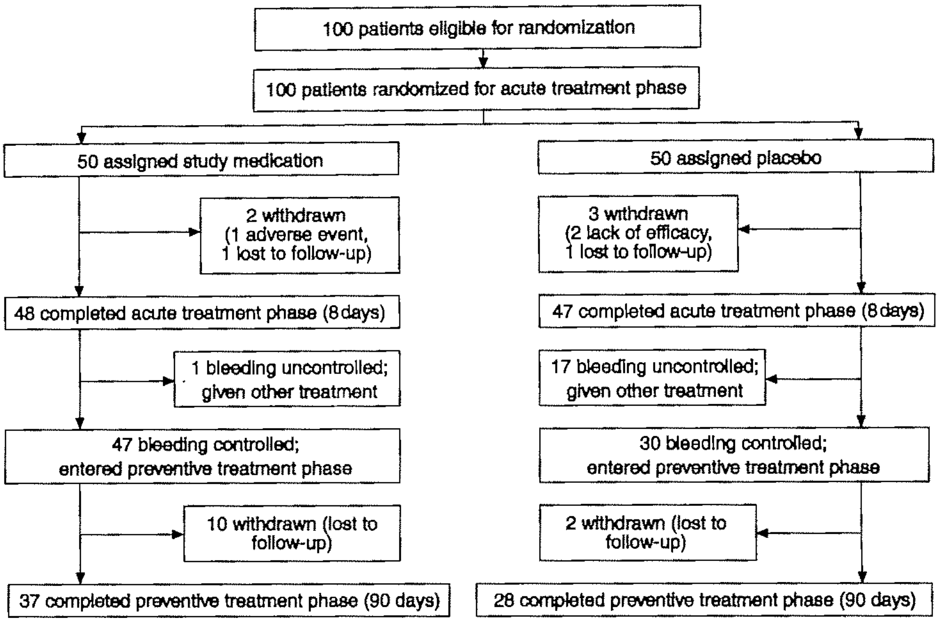
100 patients eligible for randomization
100 patients randomized for acute treatment phase
50 assigned study medication
50 assigned placebo
2 withdrawn (1 adverse event, 1 lost to follow-up)
3 withdrawn (2 lack of efficacy, 1 lost to follow-up)
48 completed acute treatment phase (8 days)
47 completed acute treatment phase (8 days)
1 bleeding uncontrolled; given other treatment
17 bleeding uncontrolled; given other treatment
47 bleeding controlled; entered preventive treatment phase
30 bleeding controlled; entered preventive treatment phase
10 withdrawn (lost to follow-up)
2 withdrawn (lost to follow-up)
37 completed preventive treatment phase (90 days)
28 completed preventive treatment phase (90 days)

Fig. 1 Study profile

Table 2 Patients with acute haemorrhoids responding to treatment with cessation of bleeding according to day of treatment

Completed treatment day	Placebo (*n* = 50)*	MPFF (*n* = 50)*	Difference in response (%)†	*P*
1	11 (22)	8 (16)	6	n.s.
2	14 (28)	22 (44)	16	n.s.
3	19 (38)	40 (80)	42 (25–59)	< 0·01
4	20 (40)	46 (92)	52 (36–68)	< 0·01
5	26 (52)	46 (92)	40 (24–56)	< 0·01
6	29 (58)	47 (94)	36 (21–51)	< 0·01
7	30 (60)	47 (94)	34 (19–49)	< 0·01

Values in parentheses are *percentages or †95 per cent confidence intervals. Treatment comprised six tablets per day for 4 days and four tablets per day for 3 days. MPFF, micronized purified flavonoid fraction, n.s., not significant

other means. Venous blood was collected from patients who completed the study to detect any change in biochemical variables assessed at baseline.

Statistical analysis

The primary outcome measure was the number of patients with no bleeding on the third completed day of treatment in the acute treatment phase. The secondary outcome measure was the number of patients in whom relapse of bleeding was prevented. Sample size was calculated to detect a 30 per cent increase with respect to the primary outcome in the number of patients responding to the study medication, that is from 30 per cent (estimated response in the placebo group)[5] to 60 per cent ($\alpha = 0{\cdot}05$, $\beta = 0{\cdot}01$). Allowing for a drop-out rate of 25 per cent during the 90-day study, it was estimated that 50 patients would be needed per group.

Response to treatment for both primary and secondary outcomes was analysed on an intention-to-treat basis. Categorical data were compared by the standard error of difference in proportions. Continuous variables were analysed with data on patients who completed the study, and changes were compared by the t test. Significance was defined as two-tailed $P < 0{\cdot}05$.

Results

Some 100 consecutive eligible outpatients, who presented as new cases, were randomized to the two treatment groups. The progress of patients through the study is shown in

Fig. 1. At inclusion, patient characteristics were similar between the two groups (*Table 1*).

The number of patients in each group who responded with cessation of bleeding in the acute treatment phase is summarized according to the treatment day in *Table 2*. The intention-to-treat analysis showed no significant difference between the groups after the first and second day of treatment. However, the response to MPFF treatment was significantly greater than that to placebo after the third day of treatment. This difference in response reached a maximum on the fourth day and decreased thereafter, but remained significant up to the end of acute treatment. The mean(s.d.) duration of bleeding (from onset to cessation) of 4·9(1·6) days in the MPFF group was less than that in the placebo group by 2·1 (95 per cent confidence interval (c.i.) 1·2–2·9) days ($P<0{\cdot}01$). Thirty patients in the placebo group and 47 in the MPFF with no bleeding at the end of acute treatment were eligible for and received preventive treatment. Intention-to-treat analysis showed that the number of patients in whom relapse of bleeding was prevented was greater with MPFF treatment by 18 (24 (95 per cent c.i. 2–46) per cent; $P<0{\cdot}05$) in comparison to placebo. The mean(s.d.) interval between cessation of bleeding and relapse was 53·1(22·7) days with the study medication compared with 34·2(22·6) days with placebo (P not significant).

The effect of treatment was not significantly different between the two groups with respect to blood pressure and biochemical variables. Mean(s.d.) compliance with medication was 97(6) per cent with MPFF and 98(5) per cent with placebo.

During the study, one patient in the MPFF group had to be withdrawn owing to gastritis on the third day of treatment. Two patients in the placebo group complained of gastritis in the preventive treatment phase but did not withdraw. No other side-effects were reported.

Discussion

Patients with first- and second-degree internal haemorrhoids and with bleeding of mild to moderate severity had clinically useful benefits when treated with MPFF in comparison to placebo. Acute bleeding ceased by the third day of treatment in the majority of patients (*Table 2*) and the total duration of bleeding was significantly reduced. After control of acute bleeding, continued treatment prevented a relapse in a significant number of patients.

The effect of MPFF in reducing bleeding has been suggested by randomized studies in comparison to placebo[5], non-micronized diosmin[7], and in open studies on pregnant[8] and non-pregnant patients[9]. However, its efficacy in completely stopping bleeding with sufficient rapidity to be of practical use in the more convenient timing of conventional invasive procedures has not been demonstrated, hence the present study.

The pathogenesis of internal haemorrhoids begins with degeneration of the connective tissue which anchors the anal cushions to the rectal wall, and their prolapse. This loss of support favours stagnation and stasis of blood in the vascular plexuses of the anal cushions[3]. It has been demonstrated that such stasis leads to a marginalization of white cells which are 'trapped' on the endothelial surface of the vessel wall[10], their activation, and release of inflammatory substances such as prostaglandins and free radicals[11]. These substances cause a sterile inflammation which leads to increased permeability, fragility and necrosis of the vessel wall[12]. The anal cushions are therefore easily traumatized by the passage of stool and bleed. The rationale behind the observed efficacy of MPFF may be related to its action of reducing stasis by increasing venous tone, suppressing inflammatory mediators, and increasing oncotic pressure and lymph flow. MPFF has been shown in an experimental study to prolong the duration of contraction of isolated rabbit vena cava in response to noradrenaline[4] and increase venous tone in normal subjects assessed by plethysmography under controlled conditions[13]. In an animal model, in which sterile inflammation was induced by subcutaneous implantation of sponge fragments, it significantly suppressed the inflammatory mediators prostaglandin E_2, $F_{2\alpha}$ and thromboxane B_2 in comparison to placebo[4], and has been shown to reduce free radical generation in a dose-dependent manner by rat neutrophils exposed to zymosan[4]. Its ability to augment oncotic pressure and lymph flow has been demonstrated in the thoracic duct of anaesthetized dogs[14]. These possible anti-inflammatory actions of MPFF are reflected in clinical studies in which it significantly reduced capillary hyperpermeability[15] and fragility[16] in comparison to placebo.

The present protocol in patients with early acute bleeding (less than 3 days at inclusion) provided a statistically efficient way of evaluating the speed and efficacy of MPFF in stopping acute bleeding and preventing relapse. Although the effects of dietary fibre were not assessed directly, the culturally determined staple food of the patients (North Indian) was unleavened bread made from unrefined whole wheat grain. In addition, about half of them were vegetarian (*Table 1*). This suggests that patients in both treatment groups were on a diet rich in fibre. The observed benefit of MPFF in comparison to placebo may therefore be over and above the possible effect of dietary fibre. The only side-effects were gastrointestinal symptoms, which were infrequent. Blood pressure and biochemical parameters were not affected by treatment, which was well accepted with a high degree of compliance.

MPFF was effective in quickly stopping the bleeding non-invasively. This could be of practical use in providing relief during the period of referral by the general practitioner to the surgeon or until such time considered convenient by the patient and surgeon for a definitive invasive outpatient procedure.

Acknowledgements

The authors are indebted to Dr David Park, epidemiological consultant; Dr Jayalakshmi Aiyengar, Dr Prashant Desai and Dr Arundhati Datye for assistance in organizing the study; Dr Reena Chakraborty for data collection; Mrs Lavita D'Souza for secretarial assistance; and Serdia Pharmaceuticals (India) Ltd for financial assistance and the study medications.

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Randomized clinical trial

Randomized clinical trial of laparoscopic *versus* open fundoplication: blind evaluation of recovery and discharge period

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Background: There is a widespread belief that introduction of the laparoscopic technique in antireflux surgery has led to easier postoperative recovery. To test this hypothesis a prospective randomized clinical trial with blind evaluation was conducted between laparoscopic and open fundoplication.
Methods: Sixty patients with gastro-oesophageal reflux disease were randomized to open or laparoscopic 360° fundoplication. The type of operation was unknown to the patient and the evaluating nurses after operation.
Results: The operating time was longer in the laparoscopy group, median 148 *versus* 109 min ($P < 0{\cdot}0001$). The need for analgesics was less in the laparoscopically operated patients, 33·9 *versus* 67·5 mg morphine per total hospital stay ($P < 0{\cdot}001$). There was no significant difference in postoperative nausea and vomiting. On the first day after operation patients in the laparoscopy group had better respiratory function: forced vital capacity 3·2 *versus* 2·2 litres ($P = 0{\cdot}004$) and forced expiratory volume 2·6 *versus* 2·0 litres ($P = 0{\cdot}008$). Postoperative hospital stay was shorter in the laparoscopic group, median (range) 3 (2–6) *versus* 3 (2–10) days ($P = 0{\cdot}021$). No difference was found in the duration of sick leave.
Conclusion: Laparoscopic fundoplication was associated with a longer operating time, better respiratory function, less need for analgesics and a shorter hospital stay, while no reduction in the duration of postoperative sick leave was found compared with open surgery.

Paper accepted 6 February 2000

British Journal of Surgery 2000, 87, 873–878

Introduction

Gastro-oesophageal reflux disease (GORD) is the most common upper gastrointestinal disease in the Western population[1,2]. The disease affects millions of people each year[2,3]. For patients with severe GORD surgical treatment is an effective way to control the gastro-oesophageal reflux. The most commonly used surgical procedure is a 360° fundoplication[4,5] which has conventionally been performed via a midline upper abdominal laparotomy. The surgical treatment aims at constructing an effective mechanism capable of preventing reflux of gastric contents into the oesophagus while maintaining the ability to swallow and belch[6]. Open surgery gives consistently good long-term results[7]. Since 1991[5,8] the application of laparoscopy to the surgical treatment of GORD has offered patients an alternative to open surgery. A number of publications have reported laparoscopic fundoplication to be effective, safe and also associated with higher patient acceptability than conventional open surgery[5,9–12]. However, these comparisons with open surgery have been based largely on the results of open surgery from the prelaparoscopic era. The aim of this study was to compare laparoscopic and open Nissen fundoplication surgery in a prospective randomized clinical trial with blind evaluation and special reference to postoperative recovery and discharge.

Patients and methods

Patients

Between April 1995 and December 1997, 94 patients underwent antireflux surgery for GORD. Thirty-two patients declined randomization and chose to be operated laparoscopically (15) or through laparotomy (17). Two patients had previous upper abdominal surgery and were excluded from the study. Sixty patients were randomized to either laparoscopic or open 360° fundoplication, 30 to each procedure. There were 17 men and 13 women in the laparoscopy group with a mean age of 46 (range 20–67) years. In the open group there were 17 men and 13 women with a mean age of 47 (range 19–76) years. All patients underwent upper gastrointestinal endoscopy and 24-h pH monitoring to establish the diagnosis of GORD and were treated with proton pump inhibitors before surgery. The study was approved by the local human studies committee and informed consent was obtained from all patients.

Design

The study was carried out as a prospective randomized clinical trial with blind evaluation, i.e. the operation method was unknown to the patient and hospital staff. Operation and anaesthesia records were kept in a sealed envelope. All patients had an equally large, close-fitted bandage and a girdle after operation. A nasogastric tube was not used in either group.

A nurse, not involved in postoperative evaluation, performed the wound inspections and dressings until the patient was discharged. All operations were performed under general anaesthesia. Alertness, pain assessment and analgesic requirements, nausea and vomiting, and antiemetic requirements were recorded after operation. Alertness was measured hourly with a four-grade scale according to the following criteria: 1, awake; 2, drowsy; 3, phlegmatic answers when spoken to; and 4, asleep, as long as the patient was in the recovery unit. Respiratory function (forced vital capacity (FVC) and forced expiratory volume (FEV)) was determined both before and after operation by means of a vitalograph (Kifa Vitalograph, Buckingham, UK) by a physiotherapist, with the patient sitting in a chair. The best result of three measurements was used. Assessment of respiratory function was made the day before surgery and on the first postoperative day with optimal pain relief. Paracetamol 1 g four times a day was given to all patients; opioid analgesics and antiemetics were administered when needed. Subjective pain appraisal was carried out by each patient using a visual analogue scale (VAS), which was also used for assessment of nausea. Patients reported their pain sensation levels during the daytime every hour when awake while in the recovery unit. On the surgical ward this was performed twice a day, morning and afternoon. Slight pain was defined as 0–3 on the VAS, moderate pain as 4–6 and severe pain as 7–10. Nausea was reported following the same scale but exchanging pain for nausea. Oral liquids were offered to the patient on day 1 and solids on day 2 after operation. The patient was discharged when ordinary food could be eaten and pain was controlled with oral analgesia. After discharge the patient visited the primary nurse once a week for a decision about further sick leave. The nurse was still unaware of type of operation and encouraged the patient to return to work when fit. If the patient still had symptoms and felt unable to return to work, the visits were repeated weekly until the patient resumed work. Information regarding sick leave was collected from the regional social insurance office.

Surgical procedures

Open fundoplication

The operation was performed according to a standardized technique and all surgeons were highly experienced in performing the procedure. The distal oesophagus was mobilized and the hiatus was narrowed with one or more posterior sutures, just enough to allow the passage of one finger through the hiatus with a 36-Fr bougie in the oesophagus. Care was taken not to divide the hepatic branch of the vagus nerve and the short gastric vessels. A 360° fundoplication was performed with the bougie in the oesophagus. The fundic wrap was sutured with three sutures that involved the front wall of the oesophagus. When the wrap was completed at least one finger should easily pass through it with the tube still in the oesophagus. The long-term results of this operation have been reported[7].

Laparoscopic fundoplication

The laparoscopic operation was performed by the same surgeons but one of the authors (F.J.) was the principal surgeon with one or two of the other surgeons as assistant. The operation was performed according to the same principles as the open operation but the fundic wrap was not sutured to the oesophagus. Furthermore, the bougie was not in place when the wrap was performed. The mode of suturing the wrap with stitches placed as far out on the greater curvature as possible was, however, the same for laparoscopic and open surgery. The 36-Fr tube was used to visually calibrate the narrowing of the hiatus.

Statistical analysis

Values were expressed as median (range). Statistical analysis was performed using the Mann–Whitney U test. $P < 0.05$ was considered to be statistically significant.

Results

Five patients in the laparoscopic group underwent conversion to open surgery owing to a large liver (one), bleeding from the oesophagus (one), trocar damage to the liver (one) and pneumothorax (two). No other complications occurred during the hospital stay and the first postoperative month in either group. All comparisons are made between the 25 patients who had a laparoscopic operation and the 30 patients randomized to open surgery. The results for patients whose operation was converted to open surgery are shown separately.

Operating time

The median duration of the operation was 148 (99–208) min in the laparoscopy group and 109 (75–174) min in the open surgery group ($P < 0{\cdot}0001$) (*Fig. 1*). In the converted group the operating time was 218 (125–310) min.

Alertness

The median value for alertness during the first postoperative hours in the recovery unit was 2 (1–4) in the laparoscopy group and 2 (1–4) in the open surgery group. There was no difference between the two groups. In the converted group the median value was 3 (2–4).

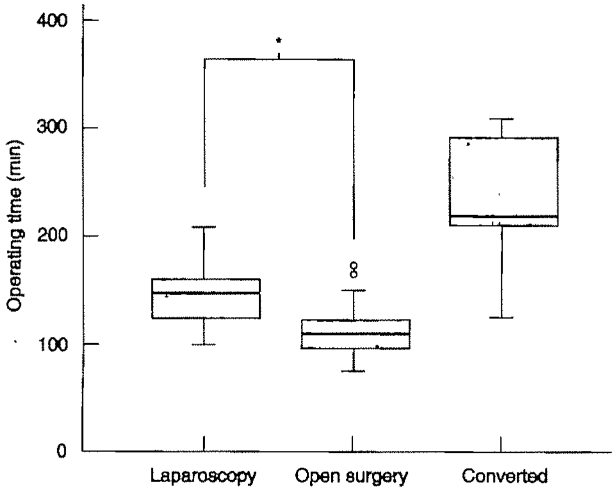

Fig. 1 Operating times. Values are median, interquartile range and range with outliers (O). $^*P = 0{\cdot}0001$ (Mann–Whitney U test)

Pain assessment, analgesic and antiemetic requirements

Pain was measured according to VAS 0–10, as presented in *Table 1*; analgesic requirements are presented in *Table 2*. Consumption of analgesic drugs was less in the laparoscopy group; however, there was no significant difference in pain assessment. Patients received either dixyrazin 2·5–10 mg or metoclopramide 5–20 mg when necessary. There was no significant difference between the two groups (*Table 2*).

Respiratory function

Preoperative respiratory function was similar in the laparoscopic and open groups (*Table 3*). After operation FEV and FVC were significantly greater in the laparoscopic group.

Hospital stay

Hospital stay was significantly shorter in the laparoscopic group: 3 (2–6) *versus* 3 (2–10) days in the open surgery group ($P < 0{\cdot}021$) (*Fig. 2*). Hospital stay in the converted group was 4 (3–7) days.

Sick leave

The sick leave duration was evaluated for 21 patients in the laparoscopy group and 24 patients in the open surgery group. The remaining patients were either students, early

Table 1 Pain assessment

	Laparoscopy ($n = 25$)	Open surgery ($n = 30$)	P^*	Converted ($n = 5$)
Recovery ward	0·25 (0–5)	2 (0–7)	0·17	1 (0–3)
Day 1	3·5 (0–6·5)	4 (2–8)	0·17	7 (6–8)
Day 2	3 (0–7)	3·5 (1·5–8)	0·07	3·25 (3–7)
Day 3	2·75 (1·5–7)	3 (0–8)	0·64	2·5 (2–5·5)

Values are median (range) on a visual analogue scale from 0 to 10.
*Laparoscopy *versus* open surgery (Mann–Whitney U test)

Table 2 Analgesic and antiemetic requirements

	Laparoscopy ($n = 25$)	Open surgery ($n = 30$)	P^*	Converted ($n = 5$)
Morphine (mg per kg per hospital stay)	0·4 (0–2·5)	0·8 (0·3–4·3)	< 0·001	0·7 (0·3–3·5)
Morphine (mg per total hospital stay)	33·9 (0–216·4)	67·5 (25·3–360·4)	< 0·001	73·2 (20·0–224·5)
Total number of antiemetic doses per hospital stay	0 (0–3)	1 (0–9)	0·14	0 (0–1)

Values are median (range). *Laparoscopy *versus* open surgery (Mann–Whitney U test)

Table 3 Preoperative and postoperative respiratory state

	Laparoscopy (n=25)	Open surgery (n=30)	P*	Converted (n=5)
Forced vital capacity (litres)				
Preoperative	4·4 (2·5–6·4)	4·2 (2·1–6·5)	0·59	3·8 (3–4·3)
Day 1	3·2 (1·5–5·7)	2·2 (1·3–3·9)	0·004	2 (1·1–2·3)
Forced expiratory volume (litres)				
Preoperative	3·7 (1·6–5·6)	3·6 (1·9–5·3)	0·79	2·5 (2·1–3·8)
Day 1	2·6 (1·1–5·2)	2·0 (0·9–3·4)	0·008	1·4 (1–1·9)

Values are median (range). *Laparoscopy *versus* open surgery (Mann–Whitney U test)

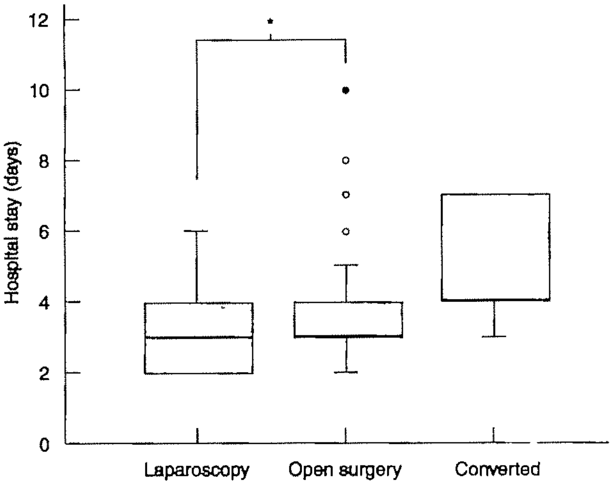

Fig. 2 Length of hospital stay. Values are median, interquartile range and range with outliers (O) and extremes (●). *P = 0·021 (Mann–Whitney U test)

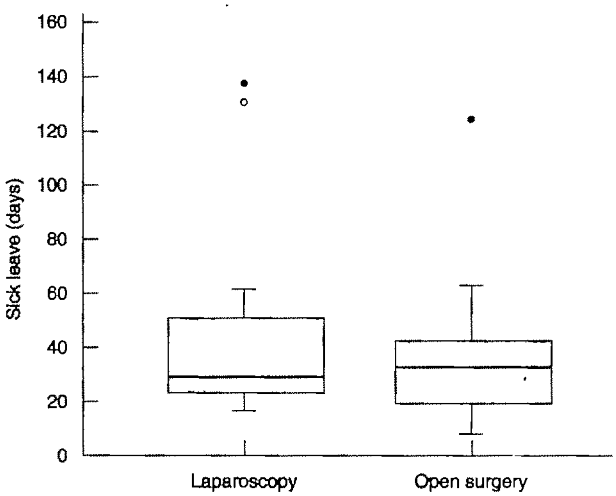

Fig. 3 Duration of sick leave. Values are median, interquartile range and range with outliers (O) and extremes (●)

retired or retired. In the laparoscopy group the median value was 27 (13–139) days and in the open group 32 (7–126) days. There were no significant differences between the two study groups (*Fig. 3*). In the converted group it was possible to evaluate two patients only, whose sick leave lasted 32 and 80 days.

Discussion

It was found that laparoscopic fundoplication leads to a longer operating time than open fundoplication, reduces the need for postoperative analgesia, and is associated with better postoperative respiratory function and a shorter hospital stay. No difference in the duration of postoperative sick leave was found between the two types of surgery.

Randomized controlled trials (RCTs) are now regarded as the definitive means of assessing the value of new surgical techniques[13]. When a new laparoscopic technique is being introduced the learning curve is considerable[14]. Performing an RCT too early in one's experience will favour the traditional technique, whereas starting it too late will favour the new technique since there is a possibility that old skills will be forgotten. The number of patients that must be included in an RCT is also important. The authors' unit is a regional reference centre at Lund University Hospital in the south of Sweden. Some 35–40 antireflux operations are performed each year. The present study was designed to include 60 patients, based on the assumption that the hospital stay would be reduced by half in the laparoscopic group. This should take about 2–2·5 years depending on the number of patients who would be willing to enter the study. There was, however, an obvious risk for a type II error in other variables. Indeed, pain assessment and need for antiemetic drugs failed to reach statistical significance despite numerical differences between the study groups. One could argue that the study should have been larger. It is, however, to the authors' knowledge, the only study with blind evaluation that has been performed to assess the outcome of laparoscopic antireflux surgery. The study was started after the unit had performed 35 laparoscopic fundoplications and the operating time had stabilized at around 150 min[15].

The correct way of analysing an RCT is to include all patients enrolled in the study, i.e. intention-to-treat analysis. In the present study, however, the analysis was per protocol, i.e. excluding patients whose operation was converted to open surgery from the laparoscopy group. This was done because the main purpose of the study was to elucidate possible advantages during the postoperative course using laparoscopic antireflux surgery. The rate of conversion in this study was comparatively high (five of 30; 17 per cent) and including these patients may have obscured any differences between laparoscopic and open surgery. It should be remembered, however, that the analysis performed favours the laparoscopic technique and that the true differences between laparoscopic and open fundoplication may be smaller than was actually found. Furthermore the small size of the study groups almost certainly predisposes to a type II error for negative results, so the results should be judged with caution. However, Laine *et al.*[11] reported few complications and good functional results from a prospective, randomized trial and noted real benefit in the recovery period, with reduced hospital stay and decreased sick leave. The study was, however, not blind and awareness of type of operation in the two study groups may have introduced bias on the part of the subjects and researchers.

In general laparoscopic surgery requires a longer operating time than open surgery. The operating time for open surgery in the present study was short compared with that in other studies[5]. The increase in operating time for laparoscopy has to be compared with the reduced postoperative requirement for opioids and faster postoperative recovery. As for the number of antiemetic doses, no significant difference was found in spite of reduced handling of the intestines in the laparoscopy group.

Because minimally invasive surgery is associated with less postoperative pain the risk of postoperative respiratory complications should be reduced. Olsén *et al.*[16] reported that morphine requirements were more than halved between laparoscopy and open surgery groups during the first 24 h, and that patients in the laparoscopy group recovered more quickly and were discharged earlier. In the present study the laparoscopy group had less reduction in FVC and FEV after operation than the open surgery group. Olsén *et al.*[16] had similar results.

There are many studies that report a shorter length of hospital stay for patients undergoing laparoscopic surgery[3,5,11,12,17]. In the present study the median value was 3 days in both groups but there were more outliers in the open group leading to a statistically significant difference. Notably, patients from the open surgery group were discharged earlier than those in other studies[5]. Watson and Jamieson[5] emphasized also that patients undergoing open surgery are being discharged earlier today than was practice in the past.

Laine *et al.*[11] reported a mean sick leave of 15 days in the laparoscopy group and 37 days in the open group. The median sick leave in the present study was 27 and 32 days respectively, and there were no significant differences between the two groups. Sick leave as an outcome measure is subject to several biases such as employment status, motivation, etc. Unfortunately, sick leave could not be evaluated in some of these patients who were in education or retired. Thus, the results must be interpreted with caution owing to the small number of patients. Another measurement of postoperative activity, such as physical activity index, could have been used. The problem is that such indices only test one of the factors that determine when a patient returns to work. Factors such as psychological problems and mental illness may occur and, after all, it is the actual return to work after surgery that is of interest.

The most important conclusion from this study is that while there are advantages with laparoscopic surgery, they are not as great as previously thought. This has implications when expanding laparoscopy into new areas of surgery.

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Original article

Preoperative portal vein embolization improves prognosis after right hepatectomy for hepatocellular carcinoma in patients with impaired hepatic function

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Background: Percutaneous transhepatic portal vein embolization (PTPE) increases the safety of subsequent major hepatectomy. The aim of this study was to determine the effect of PTPE on long-term prognosis after hepatectomy in patients with hepatocellular carcinoma (HCC).

Methods: Seventy-one patients with HCC underwent right hepatectomy between 1984 and 1998. Preoperative PTPE was performed in 33 patients (group 1) and was not used in 38 patients (group 2). Outcome after operation was compared between the groups. The patients were further divided according to the median tumour diameter (cut-off 6 cm) and indocyanine green retention rate at 15 min ($ICGR_{15}$) (cut-off 13 per cent).

Results: The cumulative survival rate was significantly higher in group 1 than in group 2 in patients with an $ICGR_{15}$ of at least 13 per cent. Tumour-free survival rates were similar in both groups. Of patients with tumour recurrence after right hepatectomy, those in group 1 were more frequently subjected to further treatment.

Conclusion: Preoperative PTPE improves the prognosis after right hepatectomy for HCC in patients with impaired hepatic function, although it does not prevent tumour recurrence.

Paper accepted 4 January 2000

British Journal of Surgery 2000, 87, 879–882

Introduction

A variety of therapeutic techniques has recently become available for the treatment of hepatocellular carcinoma (HCC)[1]. Percutaneous transhepatic portal vein embolization (PTPE) was developed to increase the safety of subsequent hepatectomy, to prevent transportal metastasis, and to increase the anticancer effect of transcatheter arterial embolization[2]. PTPE has been shown to produce atrophy of the embolized liver and compensatory hypertrophy of the non-embolized liver, even in patients with impaired hepatic function[3–5]. This increases the safety of subsequent hepatectomy[6,7]. PTPE has also been proposed as a treatment for irresectable HCC[8]. The purpose of this study was to investigate the effects of preoperative PTPE on the long-term prognosis and tumour recurrence rates after hepatectomy for HCC.

Patients and methods

The outcome was studied retrospectively in 71 patients with HCC who underwent right hepatectomy with or without preoperative PTPE between 1984 and 1998. There were 66 men and five women, with a median age of 58 years. The median tumour diameter was 6·0 cm. The median indocyanine green retention rate at 15 min ($ICGR_{15}$) was 13 per cent. Tumour extension, hepatic function and hepatitis viral infection were used to determine the necessity and desirability of right hepatectomy. Written informed consent was obtained from each patient.

Group 1 consisted of 33 patients who underwent PTPE before right hepatectomy. Group 2 comprised 38 patients who underwent hepatectomy without PTPE. In the early period of the study an attempt was made to allocate all candidates for right hepatectomy at random to the two groups. However, since the late 1980s, in the light of previous results[2,9], the indication for right hepatectomy with preoperative PTPE was extended to patients with relatively impaired hepatic function.

PTPE was performed according to previously reported methods[2]. After portography, a 5·5-Fr double-lumen balloon catheter (Herstellung und Vertrieb Medizinischer Produkte, Hamburg, Germany) was introduced under fluoroscopic control into the right portal vein through a catheter introducer (Cook Group, Bloomington, Indiana, USA). A mixture of fibrin glue (Beriplast P; Hoechst, Tokyo, Japan) and iodized oil (Lipiodol; Kodama Pharmaceutical, Tokyo, Japan) was then injected through the catheter. All patients tolerated PTPE without major complications, although transient increases in serum transaminase concentration and white blood cell count were noted.

Following PTPE the median value of the proportional volume of the right lobe was reduced from 63 to 51 per cent by 2 weeks. Right hepatectomy was performed after a median interval of 21 days. During operation, ligation of the right portal vein preceded mobilization of the right liver.

The main tumour was significantly larger in patients in group 2 (*Table 1*). The $ICGR_{15}$, alanine aminotransferase (ALAT) concentration and histological stage of fibrosis indicated significantly more advanced disease in group 1. To minimize the influence of these differences in patient background, the patients were divided into subgroups according to tumour diameter (cut-off 6·0 cm) and $ICGR_{15}$ (cut-off 13 per cent).

The results were expressed as medians with tenth and 90th centiles. Differences in the background factors between the two groups were analysed with the Mann–Whitney *U* test or Fisher's exact test. Cumulative survival rates and tumour-free survival curves were calculated using the Kaplan–Meier method. To confirm the importance of PTPE on the prognosis, Cox stepwise multiregression analysis was performed using clinical factors such as patient age, tumour size, portal venous tumour thrombus, intrahepatic metastasis, $ICGR_{15}$, ALAT concentration and preoperative PTPE. Differences in survival rates were evaluated with the log rank test. $P < 0·05$ (two-tailed) was considered significant.

Table 1 Details of patients who underwent right hepatectomy with (group 1) or without (group 2) preoperative percutaneous transhepatic portal vein embolization

	Group 1 (*n*=33)	Group 2 (*n*=38)	*P*
Median age (years)	58 (44–68)	58 (38–68)	0·95*
Sex ratio (M : F)	32 : 1	34 : 4	0·36†
Tumour factors			
Diameter of main tumour (cm)	5 (2–10)	10 (2–17)	0·003*
Portal tumour thrombus	11	21	0·094†
Intrahepatic metastasis	13	19	0·34†
Hepatic functional factors			
$ICGR_{15}$ (%)	17 (8–25)	10 (4–24)	0·001*
ALAT (units/l)	85 (39–154)	58 (31–107)	0·015*
Volume of right lobe (%)	63 (47–77)	59 (31–69)	0·077*
Histological grade of hepatitis (0–4)	2 (0–3)	2 (0–3)	0·47*
Histological stage of fibrosis (0–4)	2 (0–3)	2 (1–4)	0·039*
Status of hepatitis virus			
HBsAg+	10 of 33	14 of 37	0·62†
HCVAb+	11 of 21	15 of 29	1·0†

Values in parentheses are tenth and 90th percentiles. $ICGR_{15}$, indocyanine green retention rate at 15 min; ALAT, alanine aminotransferase; HBsAg, hepatitis B surface antigen, HCVAb, hepatitis C virus antibody. *Mann–Whitney *U* test; †Fisher's exact test

Results

The postoperative mortality rate within 30 days was one (3 per cent) of 33 in group 1 and two (5 per cent) of 38 in group 2. The cumulative survival rate was higher in group 1 than in

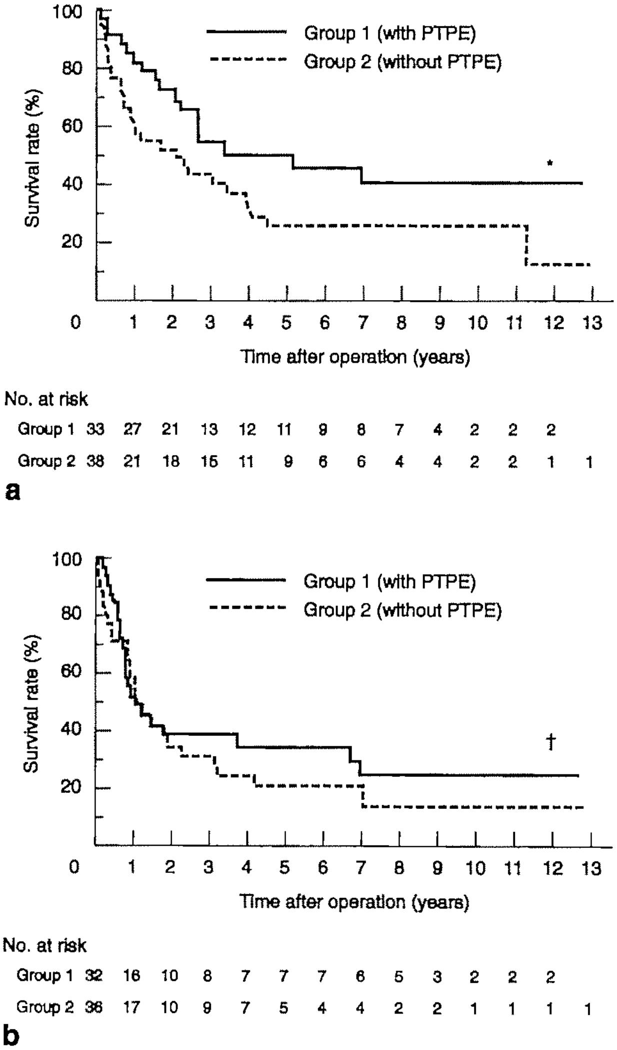

Fig. 1 a Cumulative survival rate. b Tumour-free survival rate after right hepatectomy with (group 1) or without (group 2) preoperative percutaneous transhepatic portal vein embolization (PTPE). Patients who died within 30 days of operation were excluded from tumour-free survival calculations. *$P = 0·059$, †$P = 0·60$ (log rank test)

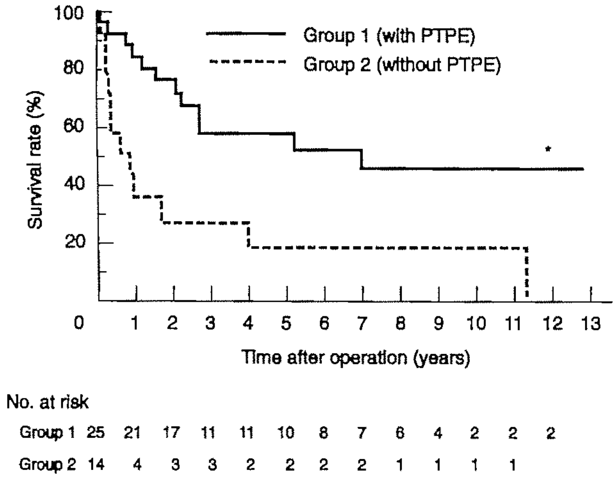

Fig. 2 Cumulative survival rate after right hepatectomy with (group 1) or without (group 2) preoperative percutaneous transhepatic portal vein embolization (PTPE) in patients with an indocyanine green retention rate at 15 min of at least 13 per cent. *$P = 0.0024$ (log rank test)

Table 2 Factors that affected postoperative cumulative survival

	Regression coefficient	Standard error	Risk ratio	P*
All patients ($n = 71$)				
Tumour size	0·058	0·029	1·060	0·044
Portal tumour thrombus	0·460	0·145	1·585	0·002
Intrahepatic metastasis	0·564	0·164	1·758	0·001
Patients with ICGR$_{15}$ ≧ 13 per cent ($n = 39$)				
Preoperative PTPE	−1·062	0·483	0·346	0·028
Tumour size	0·161	0·048	1·174	0·001

ICGR$_{15}$, indocyanine green retention rate at 15 min; PTPE, percutaneous transhepatic portal vein embolization. *Cox multiregression test using stepwise method

Table 3 Tumour recurrence and treatment after right hepatectomy

	Group 1 ($n = 22$)	Group 2 ($n = 26$)
Location		
Liver	21	20
Other	8	12
Treatment for recurrence		
Resection	8*	3*
TAE or HAI	34*	18*
PEIT or MCT	2*	6*

Values in parentheses denote the total frequency of the treatments. TAE, transcatheter arterial embolization; HAI, hepatic arterial infusion chemotherapy; PEIT, percutaneous ethanol injection therapy; MCT, microwave coagulation therapy. *Total frequency of the treatment

group 2 (*Fig. 1a*). The tumour-free survival rate, excluding patients who died within 30 days of operation, was similar in the two groups (*Fig. 1b*). The cumulative survival rate in patients in whom the ICGR$_{15}$ was at least 13 per cent was significantly higher in group 1 than in group 2 (*Fig. 2*). There were no significant differences in the tumour-free survival rate between groups 1 and 2 in any of the subgroups. Using a stepwise multiregression analysis, tumour size, portal venous tumour thrombus and intrahepatic metastasis were identified as significant prognostic factors in all patients. However, in patients in whom the ICGR$_{15}$ was at least 13 per cent, preoperative PTPE and tumour size were the significant factors (*Table 2*).

During follow-up (mean 1286 (range 13–4750) days), recurrent tumour was detected in the remnant liver or extrahepatic organs in 22 of the 33 patients in group 1 and in 26 of the 38 in group 2 (*Table 3*). Of patients with tumour recurrence, those in group 1 were more frequently subjected to further treatment than those in group 2 ($P = 0.022$, Mann–Whitney U test).

Discussion

Decisions regarding the therapeutic strategy for patients with HCC are controversial, because of the frequent coincidence of liver cirrhosis and associated infection with hepatitis viruses[10]. These factors limit the surgical options and may be responsible for multicentric tumour occurrence[11]. Over the past 15 years, the authors have attempted to define better the therapeutic strategies for patients with HCC[12]. Decisions regarding the therapeutic approach should be made after careful evaluation of tumour extension, hepatic function and status of hepatitis virus infection.

The tumour-free survival rate in the 2 years after operation, which appears to reflect the incidence of metastatic recurrence rather than multicentric recurrence, was similar in both groups. This suggests that preoperative PTPE does not prevent metastasis through the portal vein. HCC tends to invade into the portal vein at a relatively early stage. It is therefore important to prevent dissemination of cancer cells via the portal circulation during operative manipulation[13]. In the present patients, ligation of the right portal vein preceded mobilization of the right liver. Since PTPE did not improve the tumour-free survival rate, taking particular care during the operative procedure to prevent tumour dissemination may suffice to prevent iatrogenic spread of disease.

PTPE did improve the survival rate in patients with an ICGR$_{15}$ of at least 13 per cent. The survival rate after tumour recurrence was better in patients with sufficient residual hepatic function to tolerate further treatment, including second hepatic resection[12,14]. More of the patients who underwent preoperative PTPE were able to tolerate treatment for recurrent tumour, despite worse hepatic function before the original operation. Therefore preoperative PTPE may preserve hepatic function and allow treatment of tumour recurrence.

Although further prospective investigation of a large number of patients is needed, preoperative PTPE might be considered in patients with poor hepatic function who require right hepatectomy.

Acknowledgements

This work was supported by a grant for scientific research from the Ministry of Education, Science and Culture of Japan, and by a grant-in-aid from the Osaka City University Medical Research Foundation Fund.

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Pancreatic fistula after pancreatic head resection

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Background: Pancreatic resections can be performed with great safety. However, the morbidity rate is reported to be 40–60 per cent with a high prevalence of pancreatic complications. The aim of this study was to analyse complications after pancreatic head resection, with particular attention to morbidity and pancreatic fistula.

Methods: From November 1993 to May 1999, perioperative and postoperative data from 331 consecutive patients undergoing pancreatic head resection were recorded prospectively. Data were analysed and grouped according to the procedure performed: classic Whipple resection, pylorus-preserving pancreatoduodenectomy (PPPD) or duodenum-preserving pancreatic head resection (DPPHR).

Results: Pancreatic head resection had a mortality rate of 2·1 per cent; the difference in mortality rate between the three groups (0·9–3·0 per cent) was not significant. Total and local morbidity rates were 38·4 and 28 per cent respectively. DPPHR had a lower morbidity, both local and systemic, than pancreatoduodenectomy. The prevalence of pancreatic fistula was 2·1 per cent in 331 patients, and was not dependent on the procedure or the aetiology of the disease. Reoperations were performed in 3·9 per cent of patients, predominantly for bleeding and non-pancreatic fistula. None of the patients with pancreatic fistula required reoperation or died in the postoperative course.

Conclusion: A standardized technique and a continuing effort to improve perioperative management may be responsible for low mortality and surgical morbidity rates after pancreatic head resection. Pancreatic complications occur with Whipple, PPPD and DPPHR procedures with a similar prevalence. Pancreatic fistula no longer seems to be a major problem after pancreatic head resection and rarely necessitates surgical treatment.

Paper accepted 28 January 2000

British Journal of Surgery 2000, 87, 883–889

Introduction

The safety of pancreatic resection has increased in recent years, and the mortality rate has decreased to between 0 and 6 per cent in specialized units[1–4]. Large series of pancreatoduodenectomies without operative death have been reported by single institutions[5–8]. The morbidity rate after pancreatic resection is still in the range of 40–60 per cent, and many reports state that pancreatic fistulas and their septic sequelae are important contributors to surgical morbidity and mortality[9]. However, the reasons for the observed decrease in mortality rate are not entirely clear. They certainly include a perfected perioperative management and optimized care in the intensive care unit after pancreatic head resection[4], but improvements in surgical technique, attention to detail, standardized reconstruction of the gastrointestinal tract and the formation of specialized units for the treatment of pancreatic disease are crucial in this development. Data from prospective randomized trials recently demonstrated that perioperative administration of octreotide also contributed to a reduction in surgical morbidity[10–14].

This report includes three groups of patients undergoing either a classic Whipple operation, pylorus-preserving pancreatoduodenectomy (PPPD) or duodenum-preserving pancreatic head resection (DPPHR). In a prospective clinical audit, postoperative morbidity after pancreatic head resection was analysed in 331 consecutive patients with special emphasis on the prevalence of surgical complications and pancreatic fistula.

Patients and methods

A database was established to prospectively record patients with pancreatic disease. The primary aim was to determine morbidity and mortality rates after pancreatic surgery.

From 1 November 1993 to 31 May 1999 data were collected on standardized data sheets from 615 patients undergoing pancreatic resection (436 of 615) or palliative and exploratory procedures (179 of 615). The variables were grouped into demographics, indications, preoperative evaluation and risk assessment, operation and postoperative course. The present analysis includes in-hospital data for all patients undergoing pancreatic head resection during this time interval ($n = 331$).

Standard treatment protocol

Before operation, the majority of patients (97·9 per cent; 324 of 331) underwent contrast-enhanced abdominal computed tomography, typically in combination with endoscopic retrograde cholangiopancreatography (ERCP) (81·6 per cent; 270 of 331). Recently, all-in-one magnetic resonance imaging has replaced ERCP as a standard examination[15]. The extent of the pancreatic pathology and the infiltration into other organs and retroperitoneal vessels in patients with neoplasm were determined. In patients with malignant tumour, the common bile duct was decompressed by an endoscopically inserted stent in 43·3 per cent (75 of 173), corresponding to 52 per cent of patients with a bilirubin level above 40 µmol/l. In patients with chronic pancreatitis or benign tumour, 29 and 17 per cent presented with a bilirubin level above 40 µmol/l, and 8·4 and 3 per cent had an endoscopic stent inserted, respectively. Rarely, the obstructed common bile duct was decompressed by percutaneous transhepatic cholangiography and drainage (1·8 per cent; six of 331). Standard preoperative risk assessment included a stress electrocardiography and a pulmonary function test.

All patients received prophylactic antibiotics perioperatively (piperacillin 4 g, ornidazole 1 g) together with a daily dose of subcutaneous low molecular weight heparin. Octreotide was started during induction of anaesthesia and given for 7 days after operation (three doses of 0·1–0·2 mg per day subcutaneously). Perioperative and postoperative pain management included epidural anaesthesia or patient-controlled analgesia in all patients. After operation, patients were transferred to the intensive care unit overnight or to an intermediate care unit.

The surgical techniques of classic pancreatoduodenectomy (Whipple), PPPD and DPPHR have been described previously[16–20]. However, the technique of the pancreatic anastomosis is described here. Briefly, the preferred end-to-side Roux-en-Y pancreatojejunostomy to the left pancreatic remnant was created as follows. An outer layer of interrupted 5/0 polydioxanone sutures included the majority of the cut surface of the pancreas. The inner row of 5/0 polydioxanone interrupted stitches included at least three mucosa-to-duct sutures posteriorly and anteriorly. Careful attention was paid to ensure that the pancreatic duct was not obstructed to avoid postoperative acute pancreatitis. Using the same technique, an end-to-end pancreatojejunostomy including duct-to-mucosa sutures was used in a minority of cases. Pancreaticogastrostomy was not performed nor were the pancreatic or biliary anastomosis stented.

In cases of cancer, lymph node dissection along the hepatoduodenal ligament, common hepatic artery, vena cava, superior mesenteric vein and the right side of the superior mesenteric artery was a standard part of the procedure. A 12-mm 'LightFlow' capillary silicone drain (Willy Rüsch, Kernen, Germany) was placed close to the pancreatojejunostomy and brought out through the left abdominal wall to monitor pancreatic leakage. A second separate drain was left to drain the area of the hepaticojejunostomy.

Pancreatic tumours were classified according to the standards of the World Health Organization, and staged using the TNM classification system[21,22].

All complications were recorded prospectively in the database. Morbidity was determined with respect to the number of patients. However, local and systemic complications also appear in a complete list which includes all complications for all patients. The mortality rate was defined as the total in-hospital death rate. Delayed gastric emptying (DGE) was defined as the need for a nasogastric tube for more than 10 days after operation. A pancreatic fistula was defined as secretion of 30 ml or more of amylase-rich drainage fluid (more than 5000 units) per day for more than 10 days. A biliary fistula was diagnosed if there was persistent secretion of bilirubin-rich drainage fluid for more than 5 days. Bleeding was defined as the need for more than 2 units of packed red blood cells (RBCs) more than 24 h after operation, or relaparotomy for bleeding.

Statistical analysis

For comparison between the three different procedures, the results of the classic Whipple procedure were compared with those of both PPPD and the DPPHR. Statistical evaluation was carried out using two-tailed χ^2 analysis and the Mann–Whitney *U* test to determine the level of significance in unpaired groups with non-parametric distribution where appropriate. Significance was defined at the 5 per cent level.

Results

From 1 November 1993 to 31 May 1999, 436 pancreatic resections were performed. For this analysis, patients undergoing total pancreatectomy (5·0 per cent; 22 of 436), left pancreatectomy (14·7 per cent; 64 of 436) and atypical resections/tumour enucleations (4·4 per cent; 19 of 436) were excluded. All patients undergoing pancreatic head resection (75·9 per cent; 331 of 436) during this time interval were analysed in the present study. The mean age was 58 (median 58; range 18–87) years and the male : female ratio was 1 : 1·4 (137 : 194). In patients with chronic pancreatitis, malignant tumours and benign tumours of the pancreatic head the mean (median) ages were 48 (49), 64 (68) and 65 (67) years, and the male : female ratios were 1 : 0·5 (91 : 42), 1 : 0·9 (92 : 81) and 1 : 0·9 (12 : 11) respectively. The perioperative risk was assessed according to the American Society of Anesthesiologists (ASA) classification; 22 per cent of patients had a significantly raised perioperative risk, corresponding to the ASA class III group.

Patients who underwent pancreatic head resection were grouped according to the operative procedure. A Whipple procedure was performed in 25·1 per cent (83 of 331), PPPD in 40·1 per cent (133 of 331) and DPPHR in 34·7 per cent (115 of 331). The majority of patients underwent an elective procedure (98·8 per cent; 327 of 331). However, four patients underwent emergency resection for either a salvage operation after unsuccessful local resection of a pancreatic sarcoma (one), a large bleeding ulcer penetrating into the head of the pancreas (one), perforation of the common bile duct and pancreatic head during ERCP (one) or an actively bleeding tumour of the Papilla of Vater (one). *Table 1* lists the pathology results in the resected specimens.

DPPHR was carried out in 86·5 per cent of patients with chronic pancreatitis. In all patients who had DPPHR an intraoperative histological sample of the resected specimen was obtained to exclude pancreatic cancer. A Whipple procedure and PPPD were performed in 5·3 per cent (seven of 133) and 8·3 per cent (11 of 133) of patients with chronic pancreatitis. In patients with benign tumours and in malignant periampullary disease, PPPD was the preferred choice of duodenopancreatectomy in 61·7 per cent of cases. PPPD was done in 54·5 per cent of patients with pancreatic cancer (61 of 112); the remaining patients underwent a classic Whipple procedure. Of the 61 patients with malignant periampullary tumours other than pancreatic cancer, 72 per cent (44 of 61) underwent PPPD and 28 per cent had a Whipple resection. The majority of benign tumours (16 of 23) were resected by PPPD.

The intraoperative blood loss, transfusion of RBCs and operative times are given in *Table 2*. In 38·7 per cent (128 of 331) no blood or blood products were transfused during or after operation. In 9·1 per cent of patients (30 of 331) vascular structures had to be repaired or resected and reconstructed for oncological or technical reasons (*Table 2*).

Table 1 Pathology in 331 specimens after pancreatic head resection

	Malignant	Benign
Periampullary tumours		
Pancreatic	112 (33·8)	0 (0)
Ampullary	22 (6·6)	5 (1·5)
Distal bile duct	20 (6·0)	2 (0·6)
Duodenum	1 (0·3)	2 (0·6)
Cystic tumours	1 (0·3)	11 (3·3)
Neuroendocrine tumours	11 (3·3)	0 (0)
Other tumours	6 (1·8)	3 (0·9)
Chronic pancreatitis	—	133 (40·2)
Other indications	—	2 (0·6)
Total	173 (52·3)	158 (47·7)

Values in parentheses are percentages

Table 2 Details of operative procedures in 331 patients who underwent pancreatic head resection

Intraoperative data*	
Blood loss (ml)	1500(921) (100–6000)
RBC transfusion (units)	1·9(2·2) (0–15)
Operating time (min)	421(111) (220–780)
Vascular resection for tumour infiltration†	19 (5·7)
Vascular repair for technical problems†	11 (3·3)
Pancreatojejunostomy†	
End to end	34 (10·3)
End to side	294 (88·9)
Side to side	118 (35·6)‡

*Values are mean(s.d.) (range); †values in parentheses are percentages; ‡A DPPHR needs an additional side-to-side anastomosis. The technique used for the end-to-side pancreatic reconstruction is described in the text. RBC, red blood cell

Patients were in hospital for a median of 14 (mean(s.d.) 19(15); range 6–118) days and stayed in the intensive care unit or an intermediate care unit for a median of 1 (mean 2; range 1–71) day. Data related to the postoperative course are summarized in *Tables 3* and *4*. Some 61·6 per cent of patients had an uncomplicated postoperative course but, although the mortality rate was 2·1 per cent, a total local and systemic morbidity rate of 38·4 per cent after pancreatic head resection was recorded. The morbidity rate includes the 12 per cent of patients who had a postoperative course complicated by more than one local and/or systemic complication. The reoperation rate was 3·9 per cent (13 of 331) and included predominantly patients with haemorrhagic complications (four of 13) and non-pancreatic fistula (five of 13). The colonic fistulas resulted in three patients with anastomotic breakdown after segmental colon resection. In two of three patients with biliary fistula the leak was surgically repaired. None of the reoperations was done for a pancreatic fistula and no completion pancreatectomy was necessary. *Table 3* also shows that systemic complications were encountered in 19·3 per cent of patients and that cardiopulmonary complications were common (12·1 per cent).

Table 3 Deaths, reoperations and morbidity after 331 pancreatic head resections

	No. of patients	Reoperation	Death
Deaths	7 (2·1)		
Reoperations	13 (3·9)		
Total patients with complications	127 (38·4)		
Complications			
Local			
Delayed gastric emptying	54 (16·3)	1	
Septic complications	17 (5·1)		
Wound sepsis	13 (3·9)		
Intra-abdominal abscess	4 (1·2)		
Fistula	13 (3·9)		
Pancreatic	7 (2·1)		
Colonic	3 (0·9)	3	
Biliary	3 (0·9)	2	1
Bleeding	12 (3·6)	4	
Cholangitis	7 (2·1)		
Liver necrosis	3 (0·9)	1*	1
Common bile duct occlusion	1 (0·3)	1	
Small bowel obstruction	2 (0·6)	1	1
Chylous ascites	1 (0·3)		
Neurological	3 (0·9)		
Systemic			
Cardiopulmonary	40 (12·1)		3
Neurological	10 (3·0)		
Renal	5 (1·5)		
Catheter sepsis	3 (0·9)		
Other	6 (1·8)		1

Values in parentheses are percentages. *One patient was reoperated for suspected intra-abdominal sepsis, which was not confirmed intra-operatively

Fistulas remain potentially dangerous complications following pancreatic head resection. However, the rate of 3·9 per cent included all fistulas; a pancreatic fistula was encountered in 2·1 per cent of patients (seven of 331). The pancreatic fistula rate in patients with chronic pancreatitis was 2·3 per cent (three of 133) and was no different from that in patients without pancreatitis (2·0 per cent; four of 198). One patient with a pancreatic fistula presented after operation with an abdominal abscess that was drained interventionally. The remaining six pancreatic fistulas healed with initial bowel rest and prolonged administration of octreotide. In six additional patients the postoperative course was complicated by a biliary (three) or colonic (three) fistula. Five of 13 patients with a fistula required reoperation, three patients with breakdown of the colonic anastomosis and two of three patients with biliary leaks. Although the presence of a pancreatic fistula was not associated with death, one patient with a biliary fistula died late in the postoperative course, resulting in a mortality rate of 8 per cent (one of 13) in the fistula group. However, the fistula-associated mortality rate in the study overall was only 0·3 per cent (one of 331).

The mortality rate was 2·1 per cent (seven of 331). Three of the seven patients died from local complications and four as a consequence of systemic complications (*Table 3*).

The indication for pancreatic head resection in the DPPHR group was always chronic pancreatitis, and the patient population was therefore demographically and aetiologically different from that of the other two groups. With respect to reoperation and mortality rates, there were no significant differences between the three procedures (*Table 4*). The total morbidity rate was lowest after DPPHR. The differences in morbidity were significant between the Whipple group and both the PPPD and the DPPHR

Table 4 Comparison of procedures in 331 patients who underwent pancreatic head resection

	Whipple (*n* = 83)	PPPD (*n* = 133)		DPPHR (*n* = 115)	
	n	*n*	*P*	*n*	*P*
Pathology					
Neoplasia	75 (90)	121 (91·0)		0 (0)	
Chronic pancreatitis	7 (8)	11 (8·3)		115 (100)	
Other	1 (1)	1 (0·8)		0 (0)	
Hospital death	2 (2)	4 (3·0)	0·55	1 (0·9)	0·41
Complications	46 (55)	54 (40·6)	0·05	27 (23·5)	< 0·01
Local	34 (41)	40 (30·1)	0·1	18 (15·7)	< 0·01
Systemic	24 (29)	27 (20·3)	0·2	13 (11·3)	0·01
Delayed gastric emptying	27 (33)	27 (20·3)	0·04	0 (0)	0·01
Pancreatic fistula	0 (0)	4 (3·0)	0·11	3 (2·6)	0·30
Reoperation	4 (5)	5 (3·8)	0·71	4 (3·5)	0·88

Values in parentheses are percentages. PPPD, pylorus-preserving pancreatoduodenectomy; DPPHR, duodenum-preserving pancreatic head resection groups. Pancreatic fistula rates were not significantly different between the three groups. However, since DGE was the most frequent complication after pancreatoduodenectomy, and was not observed after DPPHR, the difference in morbidity is in large part explained by this complication. The Whipple group exhibited a higher DGE rate than the PPPD group ($P = 0{\cdot}04$). If complications other than DGE were analysed, the complication rates did not differ significantly, 23 per cent in the Whipple group, 20 per cent after PPPD and 24 per cent after DPPHR. Likewise, when DGE was excluded, the local morbidity was similar in the three groups ($P > 0{\cdot}12$): 8 per cent for Whipple resection, 9·8 per cent for PPPD and 16 per cent for DPPHR.

Discussion

Surgery of the pancreatic head originally had a high risk of complications, but resection is the treatment that offers the best long-term survival in patients with malignant tumours of the pancreatic head, as demonstrated in a recent study by Sener *et al.*[23] of more than 100 000 patients with pancreatic cancer. The reduced mortality rate after pancreatic resection has been a major achievement in surgery over recent decades[2–8]. The results of many centres indicate that a mortality rate below 5 per cent is a prerequisite for the performance of pancreatic resection today. Recent studies have also demonstrated that a comparable low mortality rate can be achieved in elderly patients, even in octogenarians, if the perioperative risks are assessed carefully and patients selected accordingly[8,24,25]. Pancreatic surgery should probably be concentrated in specialized units to improve quality of care and to reduce costs[26–28]. The present mortality rate of 2·1 per cent reflects the experience of other centres that perform a large number of pancreatic resections[1,2,4,7,29,30]. Pancreatic fistula and intra-abdominal abscess are still regarded as severe and relatively frequent complications that contribute substantially to the mortality rate after pancreatectomy[30]. Indeed, the pancreatic fistula rate has been reported to be above 10 per cent in several centres of excellence[7,25,31,32].

A low prevalence of local and systemic causes of death after pancreatic head resection was observed, and these causes did not include pancreatic fistula. This finding is different from that of the Johns Hopkins group which reported a 15 per cent prevalence of pancreatic fistula. The Johns Hopkins reoperation rate of 4 per cent was almost identical to that reported here, but six of nine patients reoperated for leaks of the pancreatojejunostomy died in the postoperative course[7]. Likewise, Trede *et al.*[4] reported a fatal outcome in 24 per cent of 25 patients with pancreatic leaks in a series of 557 pancreaticojejunostomies. In a recent study by van Berge Henegouwen *et al.*[33] on the outcome when pancreatic fistula followed pancreatoduodenectomy, a high mortality rate of 28 per cent was noted and early completion pancreatectomy was recommended. The present study indicates that pancreatic fistulas and their associated mortality rate could be reduced in the future if patients were to receive improved perioperative management routinely, including interventional drainage of intra-abdominal collections.

Vascular resection usually aims to increase local radicality and to obtain tumour-free resection margins. Vascular resection was performed in 5·7 per cent of patients with malignant tumours to achieve a radical (R_0) resection of pancreatic cancers predominantly infiltrating into the retropancreatic vessels. The renewed interest in vascular resection during surgery for periampullary cancer is a consequence of recent evidence that the complication rate of radical pancreatoduodenectomy is not increased in experienced hands[34,35]. Furthermore, survival after radical pancreatoduodenectomy, including segmental vein or artery resection, is similar to or better than that of standard resection[36,37].

The most frequent surgical complications after pancreatic head resection were DGE, septic complications, fistulas and bleeding. Since DGE is only observed after pancreatoduodenectomy and usually has a prevalence of 15 to over 40 per cent[8,38–40], the local and total morbidity rates after DPPHR were significantly lower than those in the other two groups. The other complications had a similar prevalence in all three groups. In patients with chronic pancreatitis, the difference in the DGE rate may have been responsible for the slower postoperative recovery after PPPD compared with DPPHR[41,42].

The septic complication rate reported here includes wound sepsis as well as intra-abdominal abscess. The prevalence of septic complications in this series was lower than that in other large series, which report a prevalence of 8–15 per cent[8,37,43]. Four intra-abdominal abscesses occurred (1·2 per cent) and were drained by an interventional radiologist in three, with full recovery.

Compared with other reports, the pancreatic fistula rate of 2·1 per cent was low, and a similar prevalence of pancreatic fistula was observed in the three procedure groups. Pancreatic fistulas were always of low output (less than 200 ml/day), were treated conservatively in six patients and interventionally in one, did not result in death and, in contrast to biliary and colonic fistulas, did not necessitate reoperation. Completion pancreatectomy for a pancreatic fistula should therefore be an exception after pancreatic head resection. Although these results contradict recommendations from other groups[31,33,44,45], many centres report a higher prevalence of fistula and intra-abdominal sepsis. Reoperation for pancreatic fistula and completion pancreatectomy may be necessary only in those with an early high-output pancreatic fistula in combination with early postoperative multiple organ failure. In contrast, the majority of biliary and colonic fistulas were managed by reoperation. One of the patients with a biliary fistula died in the postoperative period after the reoperation, giving a mortality rate of 8 per cent in all patients with a fistula.

Patients without chronic pancreatitis did not have a higher prevalence of pancreatic fistula than those with chronic pancreatitis, who had a firm, fibrotic or calcified pancreas. In both groups the rate was 2 per cent; technical factors described earlier as well as adequate perioperative management may determine the prevalence of this potentially dangerous complication. Octreotide reduces the rate of postoperative fistula after pancreatic resection and perioperative administration of octreotide is cost effective in patients undergoing pancreatic head resection[10–14]. The controversy over the routine use of octreotide in pancreatic resection may be difficult to resolve[46]. Interinstitutional comparisons may be inconclusive since differences in surgical technique may contribute significantly to postoperative results.

In conclusion, this audit confirms the findings of recent large international series that pancreatic head resection can safely be performed by either a Whipple procedure, PPPD or DPPHR, with a comparably low mortality rate in all three groups. In this study patients undergoing DPPHR had a lower local and systemic morbidity rate than those undergoing pancreatoduodenectomy, supporting the use of DPPHR in treating chronic pancreatitis. Pancreatic fistula after pancreatic head resection has become a rare complication and in general does not require reoperation. With attention to technical detail and a continuing effort to improve perioperative management, pancreatic fistula may be a vanishing problem after pancreatic head resection, and this may lead to a further reduction in surgical morbidity.

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Short note

Changing referral pattern of biliary injuries sustained during laparoscopic cholecystectomy

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Summary: More patients with less severe type biliary injury are being referred earlier to a specialist hepatobiliary unit. Most patients still have ineffective corrective surgery before transfer.

Presented in part to the European Congress of the International Hepato-Pancreatico-Biliary Association in Budapest, Hungary, May 1999 and published in abstract form as *Digestive Surgery* 1999; **16**(Suppl 1): 32
Paper accepted 17 January 2000
British Journal of Surgery 2000, **87**, 890–891

Introduction

Laparoscopic cholecystectomy has become the procedure of choice for the treatment of gallstones, but it has been reported to be associated with a higher incidence of bile duct injuries than conventional open cholecystectomy (0·6 *versus* 0·3 per cent)[1–3]. Referral of a patient with a bile duct injury to a tertiary centre is often delayed and referring surgeons frequently attempt prior surgical intervention[2,4,5]. This study was performed to evaluate changes in referral patterns that have occurred in the authors' region since the advent of laparoscopic cholecystectomy.

Patients and methods

Some 48 patients (mean age 49 years, 17 men) with a bile duct injury following laparoscopic cholecystectomy referred between January 1991 and December 1998 were analysed in two groups, before and after January 1996. The interval between laparoscopic cholecystectomy and referral; surgical, radiological, and/or endoscopic interventions; and severity of biliary injury were noted. The Strasberg classification of bile duct injuries was used; type E injuries (stricture/transection of the common/intrahepatic ducts) were the most severe, while types A (cystic/accessory duct), B, C (right aberrant duct) and D (partial circumference of common duct) represented lesser damage[1]. The Mann–Whitney *U* and χ^2 tests were used as appropriate.

Results

The incidence of bile duct injury related to laparoscopic cholecystectomy increased from a mean of 4·6 per year between 1991 and 1995 ($n = 23$) to 8·3 per year between 1996 and 1998 ($n = 25$) (*Fig. 1*). The number of type E injuries remained unchanged; less severe type A–D injuries accounted for the increase (9 *versus* 44 per cent; $P = 0·06$). The median interval to referral decreased from 32 (0–1693) to 14 (0–983) days for patients referred after 1996 ($P = 0·035$, Mann–Whitney *U* test). However, the proportion of patients undergoing reoperation before referral remained unchanged (16 of 27 *versus* 11 of 21). There was no difference in the proportion of type E injuries that underwent additional surgery before referral before and after 1996 (61 *versus* 55 per cent; $P = 0·66$, χ^2 test). Most patients required further intervention after transfer (23 of 27; 18 surgical and five radiological interventions). Four patients

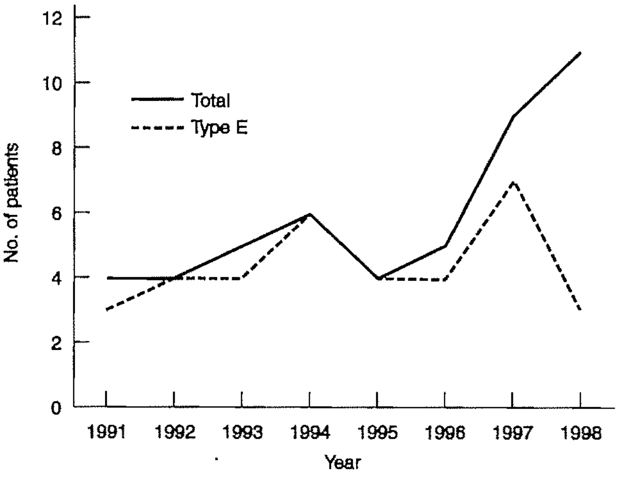

Fig. 1 Number of referrals per year of laparoscopic cholecystectomy-related bile duct injuries

died (two type E, two type A), three of whom were referred late with sepsis and multiple organ failure. The fourth patient (type E) had an associated arterial injury.

Discussion

The incidence of referral for bile duct injury following laparoscopic cholecystectomy has not decreased over the study period as might have been anticipated. Bile duct injury results in significant morbidity and mortality rates, and increased health care and litigation costs[1–6]. This study shows a rise in the number of injuries referred, although the total number of injuries within this region cannot be determined. However, the proportion of less severe (type A–D) injuries referred is rising compared with major type E injuries, which have remained constant. Frequently the full extent of bile duct damage cannot be assessed until patients undergo definitive surgery, which further supports referral of all patients with suspected bile duct injuries to a specialist unit. Two of the four deaths in this series involved patients with type A injuries who were referred late with sepsis and established multiple organ failure.

The reduction in interval between bile duct injury and referral is encouraging. Despite this trend, a majority of patients still undergo inadequate surgical reintervention (23 of 27), and most of these (18 of 27) require definitive surgery after referral. Others have reported similar results[5,6]. Stewart and Way[7] reported a success rate of 17 per cent for primary bile duct repair and zero for secondary repairs performed in non-specialist units, in contrast to 94 per cent at a tertiary centre. A similar success rate of 27 *versus* 79 per cent was reported by Carroll *et al.*[8], emphasizing the need for management of these injuries at tertiary centres.

In summary, more patients with less severe bile duct injuries are being referred earlier to a specialist hepatobiliary unit. Most patients still have ineffective corrective surgery before transfer. Following laparoscopic cholecystectomy, bile duct injury should be suspected in patients with pain, fever, bile-stained drainage fluid or deranged liver biochemistry. These findings warrant early ultrasonography to identify dilated intrahepatic ducts or bile collections, which should be drained under ultrasonographic guidance. Patients should then undergo urgent endoscopic retrograde cholangiopancreatography (ERCP); identification of a leak or failure to delineate the entire biliary tree requires prompt referral to a specialist unit. If urgent ERCP cannot be arranged, any further management should be carried out by a specialist unit.

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Original article

Prognosis and surgical management of patients with palpable inguinal lymph node metastases from melanoma

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Background: The appropriate management of melanoma metastatic to inguinal lymph nodes remains controversial. The aim of this study was to identify disease- and treatment-related factors that influence the outcome of patients undergoing therapeutic groin dissection for clinically detectable melanoma lymph node metastases.
Methods: A retrospective analysis was performed on data collected from the case records of patients who had a therapeutic inguinal lymph node dissection performed between 1984 and 1998.
Results: Some 132 patients were suitable for inclusion. Sixty patients had superficial inguinal lymph node dissection (SLND) and 72 had combined superficial inguinal and pelvic lymph node dissection (CLND). There was no difference in postoperative morbidity or major lymphoedema between SLND and CLND. The overall survival rate was 34 per cent at 5 years. On univariate analysis, age ($P = 0{\cdot}003$), the number of involved superficial lymph nodes ($P = 0{\cdot}001$) and the presence of extracapsular spread ($P = 0{\cdot}003$) were found to have a significant impact on survival. The presence or absence of pelvic lymph node metastases in patients who had CLND was a significant prognostic factor for survival (5-year survival 19 *versus* 47 per cent; $P = 0{\cdot}015$).
Conclusion: The prognosis of patients with clinically detectable melanoma metastases to the groin is variable and related to the biological characteristics of each case. CLND provided additional prognostic information and optimal regional control with no increased morbidity compared with SLND.

Paper accepted 4 January 2000

British Journal of Surgery 2000, 87, 892–901

Introduction

Previous reports of the outcome of groin dissection for melanoma have presented heterogeneous groups of patients. Patients undergoing elective, therapeutic and palliative dissection have been included in the analyses[1–5]. This has made the application of the findings to a particular clinical situation difficult. Two prognostic indices have been proposed for patients with melanoma metastatic to regional nodes[1,5]. While these studies included patients with microscopic disease they provide a useful guide for discussion of prognosis of patients with clinically detectable disease. Tumour burden in the lymph node basin, best estimated by the number of involved lymph nodes, has most consistently been found to be an important significant prognostic factor for stage III melanoma[1,4,6]. Other factors that have been found to contribute to the prognosis of patients with groin metastases include age[3,5], sex[5], ulceration of the primary tumour[2], site of the primary tumour (trunk *versus* extremity *versus* unknown)[1,4,5,7,8], clinical status of the groin[2,7,9,10], disease-free interval[2,11], extranodal extension of tumour[1,8,12], size of metastatic nodes[3] and involvement of pelvic lymph nodes[1,13,14].

The appropriate extent of groin dissection for clinically involved lymph nodes has been less clearly defined. Views of the role of combined superficial inguinal and pelvic lymph node dissection (CLND) range from therapeutic nihilism to enthusiastic advocacy. The nihilists argue that pelvic lymph node involvement equates to systemic disease and therefore dissection of pelvic nodes has no therapeutic benefit[15–18]. Further to this, CLND has been reported to result in significantly more short- and long-term morbidity than superficial inguinal lymph node dissection (SLND)[19–21]. The advocates have provided evidence to the contrary[9,11,14,22]. In a recent review there was a paucity of contemporary data to add weight to either argument[23]. The concept of selective CLND, based on clinical findings, results of computed tomography (CT) of the pelvis and frozen-section examination of the lymph nodes of the femoral canal (Cloquet's nodes), has recently been raised[4].

This study is a retrospective review of a single melanoma unit's experience with therapeutic groin dissection for melanoma with the aim of identifying disease- and treatment-related factors that influence outcome.

Patients and methods

The notes of all patients who had therapeutic groin dissection for melanoma at the Royal Marsden and Chelsea and Westminster Hospitals under the care of the senior author (J.M.T.) between 1984 and 1998 were reviewed. Patients with known systemic metastatic disease at the time of groin surgery were excluded from the study.

Data were collected on patient demographics, characteristics of the primary tumour, mode of presentation, disease-free interval, results of preoperative pelvic CT, the extent of groin surgery, the number and size of histologically positive lymph nodes, postoperative morbidity and outcome in terms of local recurrence, systemic disease-free survival and overall survival.

Therapeutic lymph node dissection has been defined as lymphadenectomy performed on patients with clinically detectable lymph node metastases and no evidence of metastatic disease. SLND involved resection of all lymph node-bearing tissue in the femoral triangle and at least 5 cm above the inguinal ligament. The nodes of Cloquet were defined as those lying within the femoral canal and were dissected as a separate specimen in some cases. CLND involved dissection of common iliac, external iliac and obturator lymph node groups followed by SLND[4]. The pelvic nodes were approached extraperitoneally through a lower abdominal wall incision. CT scans were graded according to the original reports as showing no evidence of pelvic lymphadenopathy, non-suspicious lymphadenopathy or suspicious pelvic lymphadenopathy.

For the purpose of assessing the prognostic significance of the number of histologically positive superficial nodes, results were categorized as one node positive, two to four nodes positive or more than four nodes positive[6]. Matted nodes were included in the latter group. The reporting of acute wound complications was based on documentation in the hospital record. Only one early complication was recorded for each patient. Minor wound erythema neither requiring antibiotics nor leading to prolongation of hospital stay was not recorded as wound infection. Prolonged lymph leak was defined as drainage of more than 30 ml/day for more than 2 weeks. Lymphoedema was recorded as minor if limb swelling was noted more than 3 months after operation which did not require intervention or cause interference to the patient. Major lymphoedema was defined as postoperative limb swelling persisting beyond 3 months which required active treatment or interfered with the patient's activity.

Systemic disease-free interval was calculated from the date of lymph node dissection to the date of first systemic recurrence or most recent follow-up visit. Patients were censored at the time of death when calculating this interval. Overall survival was similarly calculated from the date of lymph node dissection to death from all causes or last follow-up. Survival and systemic recurrence-free survival were compared between different groups using the log rank test, a test for trend being employed for ordered categories. Life-table curves were calculated using the Kaplan–Meier method[24]. Analysis of the effect of prognostic factors on survival and the time to systemic recurrence was undertaken using Cox regression[25]. The time from primary diagnosis to groin recurrence was analysed using the Kruskal–Wallis and Mann–Whitney tests. Comparison of proportions was undertaken with χ^2 analysis and the 95 per cent confidence intervals for proportions are exact confidence intervals.

Results

One hundred and thirty-two patients identified from hospital records were entered into the study. There were 50 men and 82 women. The median age at diagnosis of groin lymph node metastases was 56 (range 20–78) years. The distribution of the site and depth of the primary melanomas is shown in *Table 1*. In 36 patients the depth of the primary tumour was not known. In ten patients this was because there was no identifiable primary melanoma, in 14 no measurement could be made as the primary lesion had been treated elsewhere with curettage and in 12 it was not possible to obtain the original pathology results or to obtain slides for review.

The disease-free interval from diagnosis of the primary tumour to the development of clinically detectable nodal metastases is presented in *Table 1*. The disease-free interval was greater for leg and thigh primaries than for all other sites ($P < 0{\cdot}001$). Multivariate analysis was undertaken using linear multiple regression to investigate whether the difference was due to differences in primary tumour thickness at different sites. The log of the time of diagnosis of groin recurrence was used as the dependent variable (to reduce skewness), the five site groupings (anterior abdominal wall, foot, lower leg, thigh and other) were fitted as factors and the log of the primary thickness was fitted as a continuous covariate. The site of the primary tumour was still found to be predictive of the disease-free interval when thickness of the primary lesion had been allowed for ($P = 0{\cdot}001$), indicating that the difference observed was not due to differences in tumour thickness at different primary sites.

Presentation and assessment

Eighty-two patients (62 per cent) had detected a swelling in the groin. Examination of the groin at a routine follow-up visit led to the detection of lymph node metastases in 47 patients (36 per cent). In three patients groin discomfort was the reason for presentation. In 87 patients (66 per cent) a single mobile node was found on examination. Multiple mobile nodes were found in 19 patients (14 per cent) and nodes greater than 3 cm in 23 (17 per cent). Two patients presented with palpable pelvic nodes and one patient was reported to have an inguinal nodal mass with significant skin involvement. In one patient the mass was thought to be an incarcerated femoral hernia. Thirty-three patients had had an excision biopsy before referral.

CT of the pelvis was assessed in 79 patients before dissection. In nine patients scans were reported as showing pelvic lymphadenopathy suspicious of metastatic disease and in all nine the pelvic nodes were confirmed histologically to contain metastatic melanoma. In one case the CT report noted that pelvic lymph nodes were visualized but were not suspicious of metastatic disease. Metastatic melanoma was found in three pelvic lymph nodes. Sixty-nine scans were reported as showing no pelvic lymphadenopathy. Eleven of 32 patients who subsequently had a CLND following a negative CT scan had metastatic melanoma present in the pelvic lymph nodes. Three of the 38 patients who underwent SLND following a negative CT scan developed recurrence in the pelvic lymph nodes. The performance of CT of the pelvis was calculated using the 41 patients who had a pelvic CT scan before CLND. For the detection of melanoma metastatic to the pelvic lymph nodes CT had a sensitivity of 45 (95 per cent confidence interval (c. i.) 23–68) per cent (nine of 20) and specificity of 100 (95 per cent c.i. 84–100) per cent (21 of 21). The positive predictive value was 100 per cent and the negative predictive value was 66 per cent.

The median size of involved pelvic nodes when CT was not suspicious was 2·0 (range 1·0–3·5) cm and the median number of involved nodes was 1 (range 1–12). All but three patients had fewer than three involved nodes. The median size of involved pelvic lymph nodes when CT scan was suspicious was 4·0 (range 2·0–7·0) cm and the median number of involved nodes was 3 (range 1–9). The differences in involved lymph node number and size between CT-positive and CT-negative pelvic disease were significant ($P = 0{\cdot}04$ and $P = 0{\cdot}007$ respectively; Mann–Whitney test).

Operations and pattern of regional metastases

The extent of the operation performed was based on clinical suspicion of involved pelvic nodes, patient performance status, preoperative pelvic CT result and node of Cloquet status on frozen-section examination. The mean number of superficial nodes dissected was 10 (median 10 (range 1–27)). The mean number of lymph nodes containing metastatic melanoma was 2·6 (median 2 (range 0–12)). One patient had palpable pelvic disease with no superficial disease. Seventy-two patients had CLND. In 29 (40 (95 per cent c.i. 29–52) per cent) of the 72 patients the pelvic nodes contained metastatic melanoma (*Table* 2). Four of 24 patients with one superficial node involved had pelvic nodal involvement compared with 24 (51 per cent) of 47 with more than one involved superficial node ($P = 0{\cdot}01$, χ^2 test). A significant trend was also detected for increasing pelvic lymph node involvement with an increasing number of positive superficial inguinal lymph nodes ($P = 0{\cdot}04$, Mann–Whitney test). Fourteen of the 72 patients who had a CLND were reported to have had extracapsular spread of the superficial lymph node metastases. Eight of the 14 had involved pelvic nodes.

All primary sites were potential sources of metastases to both obturator and iliac lymph nodes. Twelve patients had

Table 1 Site and depth of primary tumour and time to nodal metastases

Site of primary tumour	*n*	Mean depth (mm)	Median depth (mm)*	Patients with synchronous nodes	Time to nodal metastasis (months)*†
Anterior abdominal wall	6	7·1	8·0 (3·0–8·5)	2	4 (1–5)
Back	4	5·1	5·4 (1·5–8)	0	8 (7–15)
Buttock	4	5·9	5·0 (0·8–12)	1	11 (9–96)
Foot	26	3·6	2·8 (0·4–9)	9	12 (3–100)
Lower leg	58	3·5	2·8 (0·7–9)	5	39 (4–263)‡
Thigh	20	2·3	2·0 (0·6–6·5)	0	34 (5–185)‡
Vulva	4	2·1	2·1 (0·6–3·6)	0	17 (11–40)
Unknown	10	—	—	—	—
Total	132	3·7	2·8 (0·4–12)	17	23 (1–263)

*Values are median (range). †Time to clinical appearance of lymph node metastases from the time of diagnosis of the primary tumour; excludes patients with nodal disease synchronous with primary lesion. ‡$P < 0{\cdot}001$ *versus* other sites

Table 2 Relationship of the number of involved superficial inguinal lymph nodes to the presence of pelvic lymph node metastases

Extent of SLN involvement	No. of patients	Proportion with positive pelvic lymph nodes (%)
No positive SLN	1	1 of 1
1 positive SLN	24	4 of 24
2–4 positive SLNs	32	14 of 32
>4 positive or matted SLNs	15	10 of 15
Total	72	29 of 72 (40)

Values in parentheses are percentages. SLN, superficial inguinal lymph node

Table 3 Early operative morbidity

Complication	SLND (n=60)	CLND (n=72)	Total (n=132)
Haematoma	4 (7)	3 (4)	7 (5)
Prolonged lymph leak/seroma	15 (25)	15 (21)	30 (23)
Wound breakdown	4 (7)	7 (10)	11 (8)
Wound infection	9 (15)	8 (11)	17 (13)
Total	32 (53)	33 (46)	65 (49)

Values in parentheses are percentages. SLND, superficial inguinal lymph node dissection; CLND, combined superficial inguinal and pelvic lymph node dissection

Table 4 Lymphoedema rates

Lymphoedema	SLND (n=60)	CLND (n=72)	Total (n=132)
None	38 (63)	35 (49)	73 (55)
Minor	14 (23)	20 (28)	34 (26)
Major	8 (13)	17 (24)	25 (19)

Values in parentheses are percentages. SLND, superficial inguinal lymph node dissection; CLND, combined superficial inguinal and pelvic lymph node dissection

Table 5 Site of first systemic recurrence

First site of systemic recurrence	No.
Skin/subcutaneous	14 (17)
Extraregional nodes	15 (18)
Pulmonary	18 (22)
Hepatic	6 (7)
Cerebral	17 (21)
Bone	6 (7)
GI/intra-abdominal	4 (5)
Widespread	2 (2)

Values in parentheses are percentages. GI, gastrointestinal

solitary pelvic metastases. Eleven patients had two to four involved pelvic lymph nodes and six patients had more than four nodes involved. Eighteen patients had involvement of obturator nodes. This was isolated in six cases. Twenty-three patients had involvement of iliac lymph nodes which was isolated in 11.

In 56 patients the status of Cloquet's node(s) was established by frozen-section. Twenty-six patients went on to have a CLND. Four of the five patients with positive Cloquet's nodes in this group had positive pelvic nodes. Four of the 21 patients with negative Cloquet's nodes had positive pelvic nodes. Thirty patients had SLND. One had a positive Cloquet's node but did not have a pelvic dissection for technical reasons. He developed pelvic recurrence as part of a systematic relapse at 9 months. Two of the 29 patients who had SLND following negative frozen section of Cloquet's node developed pelvic recurrence. For the purpose of this assessment these were interpreted as false negatives. Combining the data from CLND and SLND, frozen-section of analysis of Cloquet's node had a sensitivity of 45 (95 per cent c. i.17–77) per cent (five of 11) and a specificity of 98 (95 per cent c.i. 90–100) per cent (44 of 45) for the prediction of pelvic node positivity. The positive predictive value was 83 per cent and the negative predictive value was 88 per cent. In all six false-negative cases, pelvic CT had been performed and was negative.

Mortality and morbidity

There were no in-hospital or treatment-related deaths. Sixty-seven patients (51 per cent) had no procedure-related morbidity. Early postoperative morbidity is summarized in *Table 3*. There was no significant difference between the morbidity rates of SLND and CLND ($P = 0{\cdot}48$, χ^2 test). The incidence of lymphoedema is shown in *Table 4*. There was no significant difference in the rate of major lymphoedema between SLND and CLND ($P = 0{\cdot}18$, χ^2 test).

Recurrence and survival

The median follow-up from the time of groin dissection for all patients was 19 months and that for survivors was 43 (range 2–154) months. Forty-one patients were alive without systemic or regional recurrence at last follow-up. Thirteen patients were alive with regional or systemic recurrence. The median follow-up of this group was 60 (range 8–108) months. In all, 82 patients had systemic recurrence. The site of first systemic recurrence is shown in *Table 5*. The median time to systemic recurrence was 9 months from the date of groin dissection.

Four patients died from unrelated causes. Seventy-four patients (56 per cent) died from melanoma. The median

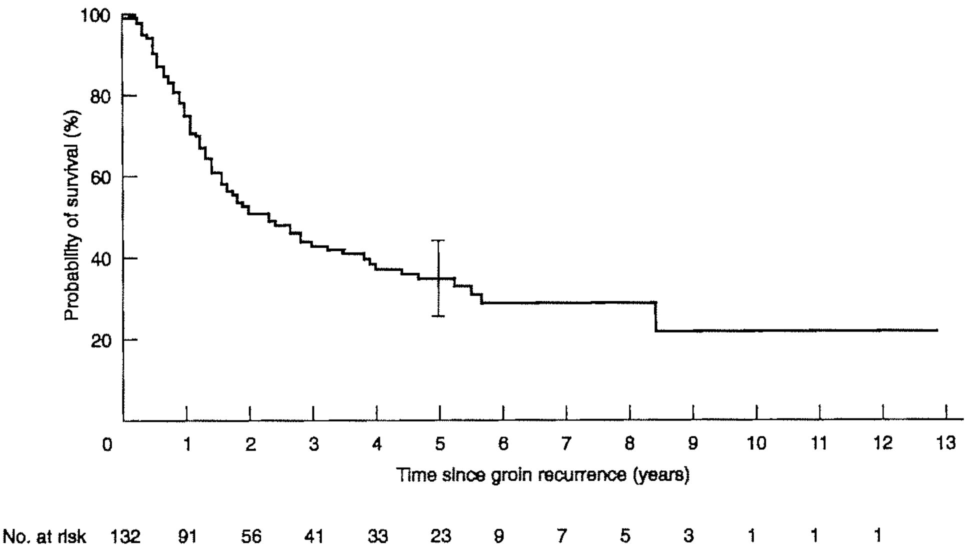


Fig. 1 Overall survival following therapeutic inguinal lymph node dissection

Table 6 Prognostic factors for overall survival and systemic disease-free survival

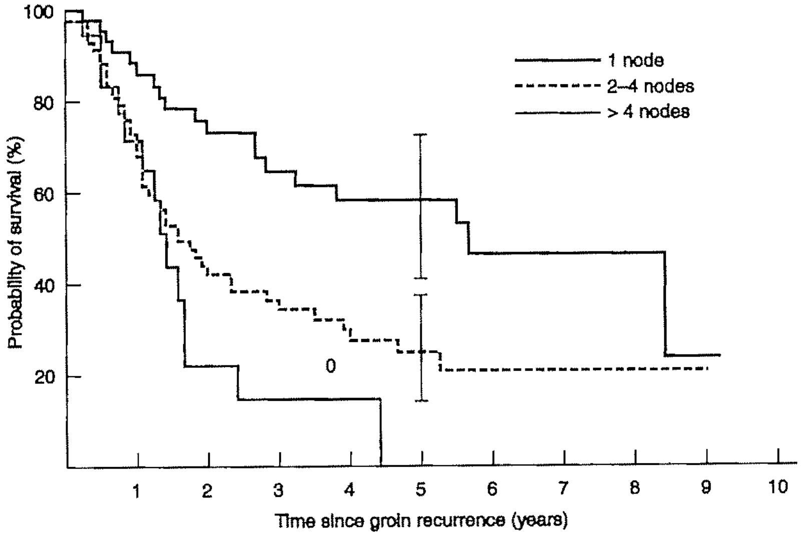
		Overall survival			Disease-free survival		
Prognostic factor	*n*	5-year rate (%)	Hazard ratio	*P*	5-year rate (%)	Hazard ratio	*P*
Primary thickness (mm)				0·07			n.s.
Unknown	36	45 (25–63)			39 (19–58)		
0·1–1·99	28	34 (15–54)			28 (12–46)		
2·0–3·99	32	36 (19–53)			30 (15–47)		
≥ 4·0	36	26 (12–43)			27 (12–45)		
Operation				n.s.			n.s.
SLND	60	34 (21–48)			36 (22–50)		
CLND	72	36 (24–48)			27 (16–39)		
Sex				n.s.			n.s.
Male	50	36 (21–50)			28 (14–44)		
Female	82	34 (22–46)			32 (21–44)		
Age (years)				0·003			n.s.
< 60	94	43 (31–53)			34 (23–45)		
≥ 60	38	11 (2–28)			16 (3–37)		
Disease-free interval (months)				n.s.			< 0·05
0–12	64	26 (14–39)			20 (10–34)		
13–48	38	34 (19–50)			34 (19–50)		
≥ 49	30	52 (31–70)			43 (22–62)		
Primary site				n.s.			n.s.
Thigh/leg	78	35 (24–47)			33 (21–45)		
Other	54	34 (19–48)			26 (13–44)		
Extracapsular spread				0·003			n.s.
Yes	27	18 (6–36)	1·9 (1·1–3·2)		27 (10–47)		
No	105	39 (28–49)			32 (22–42)		
No of positive superficial nodes				0·001			< 0·001
1	45	58 (41–72)			42 (26–58)		
2–4	68	25 (14–37)	1·9 (1·4–2·7)		27 (15–40)	1·8 (1·3–2·5)	
> 4/matted	18	11 (1–35)	3·7 (2·6–5·2)		0	3·1 (2·2–4·4)	

Values in parentheses are 95 per cent confidence intervals. SLND, superficial inguinal lymph node dissection; CLND, combined superficial inguinal and pelvic lymph node dissection; n.s., not significant

survival was 15·5 months from groin dissection to death from melanoma. Three of these patients died from uncontrolled pelvic disease without evidence of systemic disease. Seventy-four per cent of melanoma-related deaths occurred within 24 months of groin dissection and 95 per cent had occurred within 5 years.

The overall actuarial 5-year survival for all patients was 34 (95 per cent c.i. 25–44) per cent (*Fig. 1*). The 5-year survival rate was 36 per cent for patients having CLND and 34 per cent for those who had SLND.

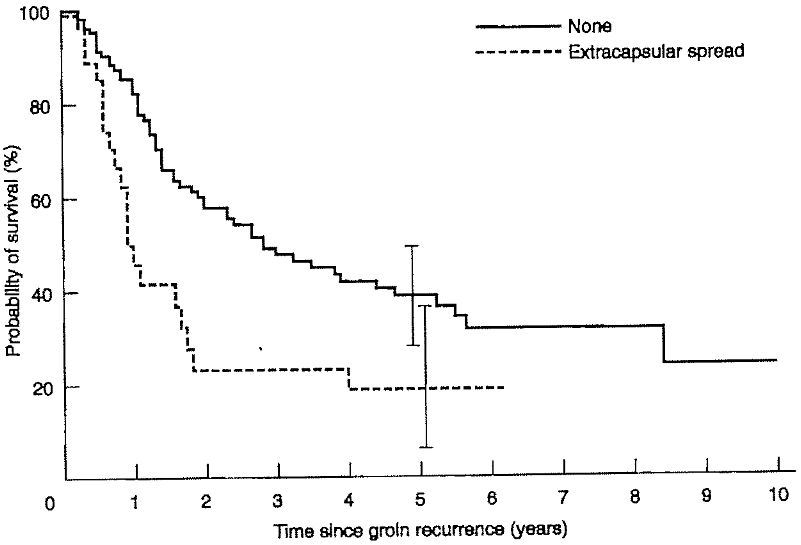
Univariate analysis of prognostic factors that influenced overall and systemic disease-free survival following detection of palpable melanoma metastases to inguinal lymph nodes is presented in *Table 6*. On multivariate analysis the



No. at risk

1 node	45	34	28	22	17	13	6	5	3	1
2–4 nodes	68	44	23	17	13	8	2	1	1	0
> 4 nodes	18	12	4	2	2	0	0	0	0	0

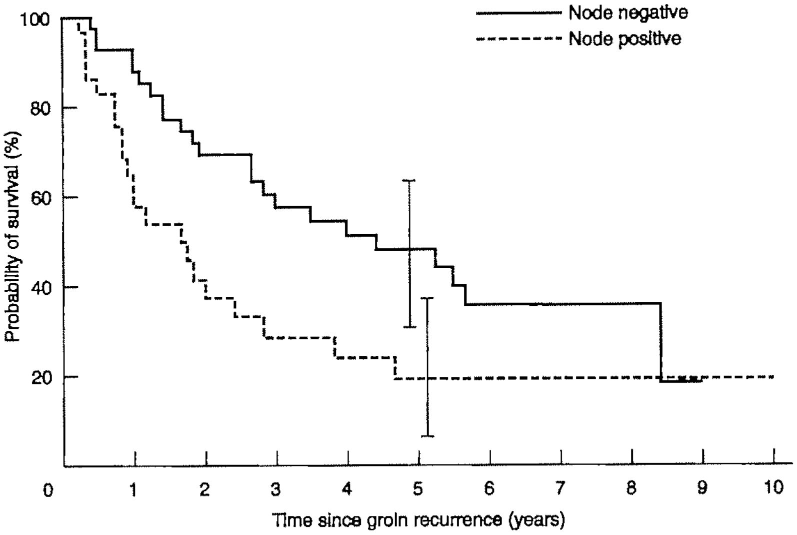
Fig. 2 Survival according to the number of positive superficial inguinal lymph nodes. $\chi^2 = 15{\cdot}37$, 2 d.f., $P = 0{\cdot}000$



No. at risk

No spread	105	79	51	36	28	28	7	5	3	1	1
Extracapsular spread	27	11	5	5	1	1	0	0	0	0	0

Fig. 3 Survival according to the presence or absence of nodal extracapsular spread. $\chi^2 = 9{\cdot}13$, 1 d.f., $P = 0{\cdot}003$



No. at risk											
Node negative	43	35	26	19	17	14	8	5	3	1	1
Node positive	29	17	9	6	5	4	1	1	1	1	0

Fig. 4 Survival according to pelvic lymph node status. $\chi^2 = 5{\cdot}88$, 1 d.f., $P = 0{\cdot}015$

number of positive superficial nodes ($P < 0{\cdot}001$) and the presence of extracapsular spread ($P = 0{\cdot}02$) remained significant prognostic factors for overall survival. The effect of these factors is presented in *Figs 2* and *3*. The number of positive superficial nodes was the only independent factor for systemic disease-free survival. The prognostic significance of pelvic lymph node metastases was assessed in the 72 patients who underwent CLND (*Fig. 4*). The estimated 5-year survival rate for the 43 pelvic node-negative patients was 47 (95 per cent c.i. 30–63) per cent compared with 19 (95 per cent c.i. 6–37) per cent for the 29 node-positive patients ($P = 0{\cdot}015$). Pelvic nodal status, categorized as positive, negative or unknown (i.e. SLND), maintained significance when assessed in the multifactorial analysis of all 132 patients. Patients with known negative pelvic nodes faired better than those who underwent SLND, who faired better than patients with known positive pelvic nodes (hazard ratio 0·6, 1·0 and 1·6 respectively; $P = 0{\cdot}02$).

Groin recurrence occurred in 25 patients. In 17 patients this was restricted to skin and subcutaneous tissues. Pelvic node recurrence occurred in one of 72 patients who had CLND and seven of 60 patients who had SLND ($P = 0{\cdot}01$, log rank test).

Discussion

This study contributes to two broad areas of discussion in regard to therapeutic groin dissection for clinically detectable melanoma metastases. First, it gives an accurate description of the natural history and prognosis of this well defined group of patients. Earlier studies have presented a broader spectrum of disease by including elective and palliative dissections[1–5]. Although not yet included in the literature, patients who have selective lymph node dissection following positive sentinel node biopsy need to be regarded as a distinct clinical group. Second, this study examines the risks and benefits associated with the extent of dissection performed for palpable melanoma metastases to inguinal lymph nodes.

Univariate and multivariate analysis was performed on a range of readily assessable factors to determine their influence on overall survival and systemic disease-free survival. The median follow-up of survivors of 43 months was beyond the median time to melanoma-related death which suggests that the number of events not recorded because of inadequate follow-up is small. Using univariate analysis, significant prognostic factors for 5-year survival included age, the presence or absence of extracapsular spread of lymph node metastases and the number of positive superficial inguinal lymph nodes. Disease-free interval and the number of positive superficial nodes were the only significant factors influencing systemic recurrence. The impact of the number of positive superficial nodes on survival is a consistent finding and has been well reviewed by Buzaid *et al.*[6]. Extracapsular spread was the most significant factor on multivariate analysis in a review by Coit *et al.*[1] of 350 cases of axillary and inguinal stage III melanoma. Balch *et al.*[2] analysed 185 patients with stage III disease and found that primary melanoma ulceration and unknown primary site were significant determinants of survival. Patients with an unknown primary site faired better than those with other primary sites. The number of patients with unknown primary tumours in the current study was too small to assess and ulceration of the primary lesion was not assessed because of a lack of reliable reporting.

Slingluff *et al.*[5] studied the outcome of 1273 patients with nodal metastases. A prognostic index was formulated and included not only nodal number but also sex, age, site, primary thickness and disease-free interval. The present authors observed that younger age and longer disease-free interval did have some impact on survival although these factors were not statistically significant; a trend towards a difference in survival between the sexes was not observed. The primary site did not impact on overall survival in this study. Interestingly, patients with leg and thigh primary tumours took significantly longer to develop nodal metastases than those with primaries at other sites. This was independent of thickness of the primary lesion. While this observation has no influence on prognosis, it does suggest a biological difference between melanomas at different sites. The status of pelvic lymph nodes dissected at CLND provided additional prognostic information. This was independent of other significant prognostic factors on multifactorial analysis. The importance of pelvic node status has been overlooked in previous multifactorial analyses. The disease free interval between groin dissection and systemic recurrence was similar to previous reports[1,26].

The issues to consider when deciding upon the extent of groin dissection for palpable nodal metastases are the potential therapeutic benefit and the morbidity of each procedure (SLND and CLND). The therapeutic benefit of CLND has been strongly advocated by Karakousis *et al.*[9,11,27] and is supported by the extensive experience of the Netherlands Cancer Institute[22,28]. The argument is based on 5-year survival estimates for patients with positive pelvic nodes ranging from 24 to 35 per cent. The present results are less encouraging; a 95 per cent confidence interval for survival was calculated, giving a more realistic estimate (5-year survival rate 6–37 per cent). The results of all but two previous studies fall within this range[9,11,13–17,22,28–30]. Overall it appears that a quarter of patients with pelvic lymph node metastases may benefit from CLND. Studies with survival results at the lower end of the range have not supported a therapeutic benefit of CLND as pelvic metastases have been interpreted as a marker of systemic disease. To date the dilemma has not been resolved as a randomized controlled trial has not been performed to compare SLND with CLND.

In the present analysis there was no difference in survival between patients undergoing SLND and CLND. Mann and Coit[4] compared SLND with CLND in patients matched in their risk profile for pelvic nodal disease and did not find a survival benefit from CLND. There are two explanations for the present findings. First, it is possible that CLND had no therapeutic benefit. Second, CLND may have had a therapeutic benefit that was not detected because of selection bias. The possibility of selection bias is supported by a number of indirect observations which suggest that the number of patients with pelvic node disease, and therefore worse prognosis, was likely to have been significantly greater in the CLND group. First, the rate of pelvic node positivity in patients undergoing CLND was significantly greater than expected based on the cumulative incidence of pelvic node positivity at therapeutic groin dissection reported in the literature (40 *versus* 28 per cent)[23]. Second, the pelvic node recurrence rate in the SLND group (12 per cent) was less than expected. Third, the overall incidence of pelvic node disease, either at CLND or as a pelvic recurrence following SLND, was 36 (27 per cent) of 132, as would be predicted from published reports. Given the deleterious effect that pelvic lymph node metastasis has on survival, it is speculative, but not unreasonable, to argue that the group of patients who had CLND should have had a worse survival rate and that this was balanced by the therapeutic benefit of CLND.

There are two main arguments against CLND. First, the 5-year survival rate of patients with pelvic node disease has been reported in some series to be in the order of 0–20 per cent[13,15–17,29,30]. As stated earlier, the authors of these studies have concluded that pelvic nodal disease is a marker of systemic disease and that pelvic node dissection in an attempt to cure the disease is futile. Furthermore, pelvic nodal recurrence has not been thought to be a significant problem after SLND. However, if one assumes an estimated rate of pelvic nodal involvement of 30 per cent for patients with clinically detected inguinal nodes and a 5-year survival rate of 20 per cent when the pelvic nodes are positive, then CLND would benefit 6 per cent of patients with superficial inguinal lymph node metastases, in regards to long-term survival. Selection of patients with a high likelihood of pelvic node disease would improve the survival benefit of CLND.

The second major criticism of CLND has been the belief that the procedure results in greater morbidity. In a recent review it was found that there was little evidence to support this notion[23]. The available evidence for comparison is difficult to interpret because there are few objective reports and no prospective controlled trials[19,27,31,32]. While post-operative morbidity rates were high for both SLND and CLND in the present study there was no significant difference between the operations. Lymphoedema continues to be a major concern; the incidence of major lymphoedema following CLND was not significantly higher than that following SLND, although there was a trend towards a lower rate following superficial dissection.

In the authors' experience most patients should expect limb swelling in the first 3–6 months after operation, especially in the thigh. The incidence of lymphoedema restricting activity beyond 6 months has been surprisingly low in most series[27,31,32]. Thus there was little evidence in this study to suggest that CLND should be avoided on the basis of increased morbidity.

The therapeutic benefit of CLND has largely been compared with SLND in terms of survival. Local disease control is another important consideration. The rate of pelvic nodal recurrence has rarely been reported and wound recurrence has not been differentiated from pelvic recurrence[4,16,17]. In the present study, wound recurrence had a definite correlation with in-transit disease but not with the extent of surgery. It would appear that recurrence in and around the groin wound is a function of the disease rather than the extent of groin dissection. Singletary *et al.*[17] reported only one troublesome pelvic recurrence in 133 SLNDs. However, the study population consisted of many elective lymph node dissections and the pelvic nodal involvement rate in the CLND group was only 4 per cent. Two reports have demonstrated an increased rate of pelvic node recurrence following SLND similar to the present findings[4,33]. Mann and Coit[4] did not encounter difficulties with management of nodal recurrence as it was either an asymptomatic part of systemic recurrence or was managed successfully by further surgery. This was true for five of the present patients but not for three who died from uncontrolled pelvic disease following SLND.

The rate of pelvic nodal recurrence was very low in the CLND group. This was achieved through the use of thorough nodal dissection including the obturator nodes in all cases, as recommended by Karakousis *et al.*[34]. In 18 of the 29 patients with pelvic nodal disease the obturator nodes were involved. It was decided not to divide the inguinal ligament and the pelvic nodes were approached through the abdominal wall. The theoretical risk of tumour dissemination caused by division of the specimen at the inguinal ligament was not supported in these results.

A means of selecting patients at high risk of pelvic nodal disease to pelvic lymph node dissection would potentially maximize any therapeutic benefit of the procedure. It would also allow low-risk patients to avoid exposure to a more extensive procedure. The extent of superficial inguinal lymph node involvement provided a guide to the status of the pelvic nodes. The results were consistent with those of other reports[4,13,16,35]. Patients with one positive superficial node have a risk of pelvic nodal involvement of approximately 10–20 per cent. This rises to 30–50 per cent for two to four nodes and 60–70 per cent for more than positive four nodes. Matted superficial nodes and the presence of extracapsular spread also indicate a high risk of deep nodal involvement. In practical terms this information is only available after the operation has been completed and would require a second procedure in selected cases. In addition, it may be that patients with minimal superficial disease and positive pelvic nodes would most likely benefit from CLND[13].

The performance of preoperative CT of the pelvis for the detection of nodal metastases has not been studied extensively[4,35]. In this study CT was able to detect more extensive pelvic nodal disease, but the overall sensitivity was poor. Peroperative frozen-section analysis of the lymph nodes of the femoral canal has been assessed as a marker of pelvic nodal involvement with mixed results[4,16,36]. As with CT the results show a low sensitivity. Positron emission tomography (PET) has been assessed in one study; the sensitivity for detection of superficial nodal metastases was 85 per cent and the specificity was 91 per cent in a group of 24 patients[37]. These results are encouraging and indicate that PET should be assessed as a method of selection of patients for CLND.

In conclusion, the prognosis of patients with clinically detectable melanoma metastases to the groin is variable and related to the biological characteristics of each case. The differences in biological character are best estimated by the number of involved superficial inguinal lymph nodes and the presence or absence of extracapsular spread of the nodal metastases. In this study CLND provided additional prognostic information with no increased morbidity compared with SLND. CLND resulted in significantly less regional recurrence, but an overall survival benefit was not demonstrated.

Acknowledgements

The authors thank Dr S. Retsas, Medical Oncologist, Charing Cross Hospital, London for assistance with follow-up data for some patients. This work was funded by the Royal Marsden NHS Trust Melanoma and Sarcoma Research Fund.

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Experimental study of faecal continence and colostomy irrigation

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Background: Colostomy irrigation is a useful method of achieving faecal continence in selected conditions, but remains largely underutilized because it is time consuming. This study investigated the effect of modifying irrigation technique (route, infusion regimen and pharmacological manipulation) on colonic emptying time in a porcine model.

Methods: An end-colostomy and caecostomy were fashioned in six pigs. Twenty markers were introduced into the caecum immediately before colonic irrigation. Irrigation route (antegrade or retrograde), infusion regimen (tap water, polyethylene glycol (PEG), 1·5 per cent glycine) and pharmacological agent (glyceryl trinitrate (GTN) 0·25 mg/kg, diltiazem 3·9 mg/kg, bisacodyl 0·25 mg/kg) were assigned to each animal at random. Colonic transit was assessed by quantifying cumulative expelled markers (CEM) and stool every hour for 12 h.

Results: Mean CEM at 6 h for bisacodyl, GTN and diltiazem were 18·17, 12·17 and zero respectively; all pairwise differences in means were significant ($P < 0.001$). The difference at 12 h between the two routes ($P = 0.001$) and three fluids (tap water 6·75, glycine 14·83, PEG 16·33; $P < 0.001$) was significant, but not for PEG *versus* glycine and bisacodyl *versus* GTN. Cumulative output was significantly more with the antegrade than retrograde route using PEG, but the difference in mean cumulative output for bisacodyl and GTN at 12 h was not significant.

Conclusion: Colonic emptying is more efficient with antegrade than retrograde irrigation. PEG and glycine enhance emptying similar to bisacodyl and GTN solution. These findings show promise for improved faecal continence by colostomy irrigation and may justify construction of a Malone conduit at the time of colostomy in selected patients who wish to irrigate.

Presented in part to the British Society of Gastroenterology in Glasgow, UK, March 1999, and published in abstract form as *Gut* 1999; 44(Suppl 1): A135

Paper accepted 20 January 2000

British Journal of Surgery 2000, 87, 902–908

Introduction

Colostomy irrigation was conceived over 200 years ago by Duret, who fashioned an 'artificial anus' in an infant with bowel obstruction and instituted colonic cleansing using simple water containing two drops of syrup of rhubarb[1]. Despite initial criticism in the UK[2–4], this simple technique has established a useful clinical role, giving fewer stoma actions and allowing some people to dispense with bulky appliances and medication, with improved quality of life[5,6].

Studies comparing irrigation with spontaneous evacuation (dietary or drug regulation of stoma action with an appliance to retain faecal discharge) are few, but indicate that the former consistently achieves superior levels of continence[6–9]. In one series, full continence over 24–48 h was achieved in 97 per cent of participants[10]. However, the overwhelming majority of people with a colostomy do not perform irrigation because it is time consuming (1–2 h) and may be ineffective, with episodes of faecal discharge between washouts. Techniques that might reduce irrigation time, make it more efficient and thereby broaden its appeal among people with a colostomy may reduce its unpopularity.

This study was designed to investigate the effect of modifying irrigation technique on colonic emptying time in a porcine model. First, a comparison of antegrade and retrograde irrigation was undertaken to determine the more efficient approach. Second, alternative infusion regimens were tested to determine whether any conferred an advantage over the generally recommended tap water. Finally, the outcome of pharmacological manipulation with glyceryl trinitrate (GTN) and diltiazem solutions was evaluated in contrast with bisacodyl (positive control).

Materials and methods

This study was performed under an animal licence granted by the Home Office. Following 12 h of water and diet restriction, laparotomy was performed in six pigs (Large White Landrace Crossbreed, 26–33 kg) under general anaesthesia (halothane 1·5 per cent in 4 litres oxygen and 1 litre nitrous oxide per min). All animals were sedated beforehand with xylazine 1 mg/kg and ketamine 5 mg/kg; intramuscular ampicillin 500 mg and intravenous metronidazole 250 mg was given as perioperative antibiotic prophylaxis. An end-sigmoid colostomy was fashioned and a caecostomy established by locating the taenia coli at the base of the caecum and, through a stab incision, securing a 24-Fr entrafeed gastrostomy tube (Medicina, Berkshire, UK) with a purse-string using 3–0 vicryl sutures. In the immediate postoperative period, analgesia was provided by subcutaneous injection of carpofen 4 mg/kg twice daily and animals were recovered in isolation so that their wounds could be protected with specially applied dressings. Basic caloric requirement was provided by intracolonic infusion of 150 ml Lectade Plus (Pfizer, Sandwich, Kent) twice daily until oral fluids were tolerated. By the end of a 10-day observation period, all animals were fully mobile, wounds had healed completely and normal dietary intake had been restored.

Colostomy irrigation

On the morning of irrigation animals were weighed and then lightly anaesthetized by inhalation of 1 per cent halothane in oxygen at 4 l/min in the operating theatre. An adhesive base plate of a two-piece stoma appliance (Dansac Unique 2 Flexi 55 mm; Dansac, Histon, Cambridge) was then sited over the end-colostomy and reinforced with a circumferential continuous suture (0 silk) through the skin and edge of the base plate. Twenty coloured hollow beads (James Galt & Co Ltd, Cheshire, UK), measuring 0·5 mm in diameter, were introduced as markers into the caecum via the caecostomy tube immediately before irrigation. Two methods of colonic washout (antegrade and retrograde) and three fluid regimens comprising tap water, polyethylene glycol (PEG) (Norgine, Middlesex, UK) and 1·5 per cent glycine (Baxter Healthcare, Norfolk, UK) provided six treatment combinations. A Graeco-Latin square was used to assign the six combinations at random, such that each treatment was studied once in each of 6 weeks and once in each animal. All six animals therefore each received a combination of the two treatments over 6 weeks, one combination per week. Colostomy irrigation was performed by introducing 500 ml of a given fluid into the end-colostomy (retrograde) or caecum (antegrade) from a height 1 m above the animal. Once inflow of fluid into the colon was complete, a stoma bag was attached to the base plate and animals were returned to their pens. Hourly retrieval of samples (faecal effluent and markers) from the stoma bag was commenced in each animal for a total of 12 h.

Using the same replicated Graeco-Latin square, three drugs were evaluated: GTN 0·25 mg/kg by intravenous injection (David Bull Laboratories, Warwick, UK), diltiazem 3·9 mg/kg (Adizem-60 tablets; Napp Laboratories, Cambridge, UK) and bisacodyl 0·25 mg/kg (Dulcolax suppositories; Windsor Healthcare Limited, Windsor, UK) added to 500 ml tap water. The drugs were assigned at random to each animal. Each drug solution was studied twice a week for 3 weeks and once in each animal. In this experiment, antegrade irrigation was performed in all cases; recovery, frequency and duration of sample collection was as described previously.

Measurement of transit

The effect of irrigation method, fluid type and pharmacological agents on colonic emptying time was assessed by quantifying expelled markers and stool. On each occasion, this was estimated by counting the number of markers in the stoma bag at intervals of 1 h, recorded as cumulative expelled markers (CEM). In addition, the amount of faecal effluent (in grams) each hour was calculated and expressed as a percentage of body-weight (percentage cumulative output) to account for the variation between animals.

Statistical analysis

Analysis of variance (ANOVA) was performed on data obtained from samples collected at 6 and 12 h. The mean, difference in mean values and 95 per cent confidence intervals were calculated for expelled markers and faecal effluent and $P < 0.05$ was considered significant.

Results

Six pigs were used in this study and provided a total of 54 observations over 9 weeks. There were 36 observations for the irrigation approach, either antegrade (18) or retrograde (18), and 36 for the infusion regimen, PEG (12), 1·5 per cent glycine (12) or tap water (12). The remaining 18 observations related to the influence of GTN (six), diltiazem (six) and bisacodyl (six).

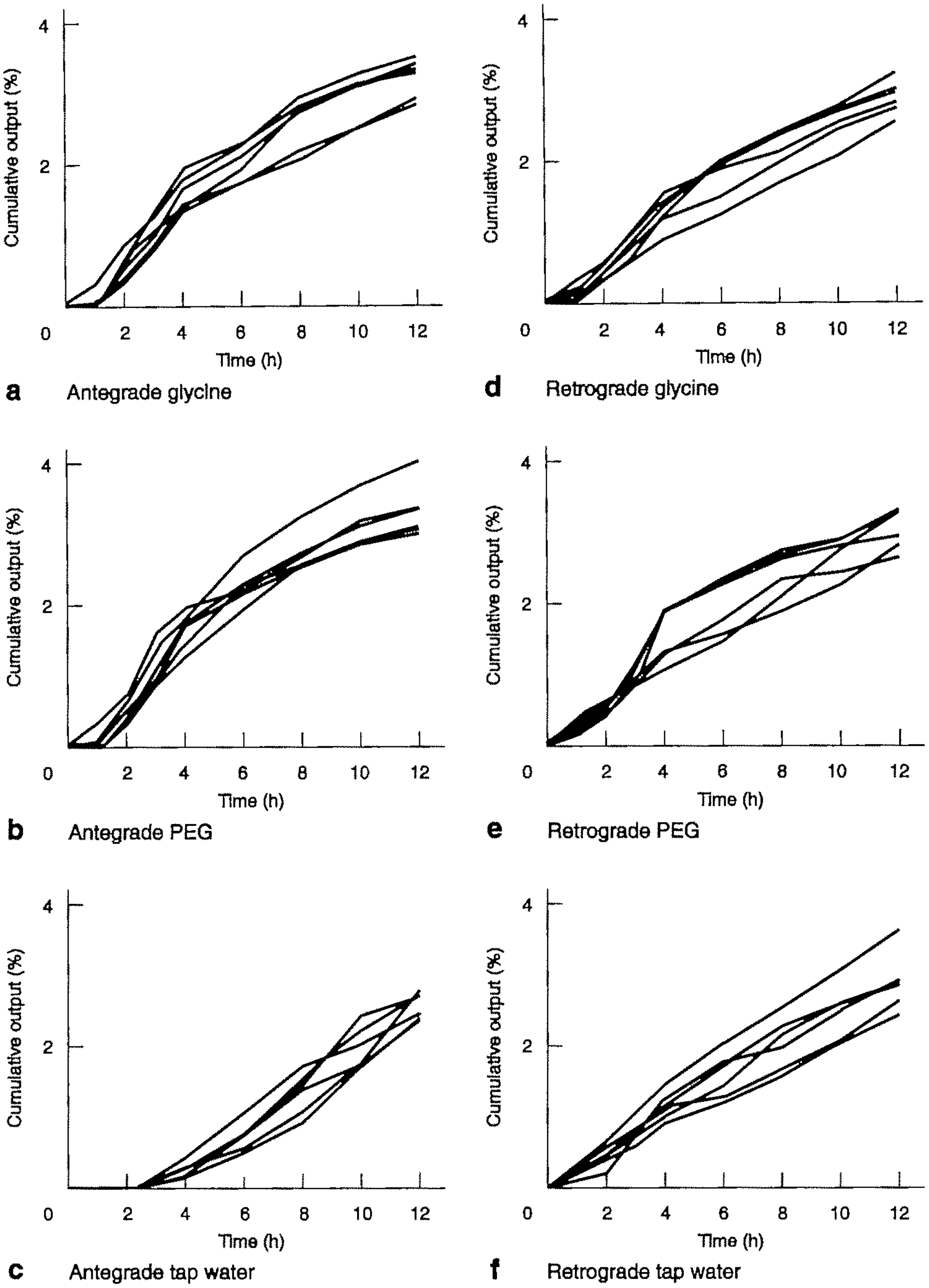


Fig. 1 Cumulative faecal output for antegrade (a–c) and retrograde (d–f) irrigation with glycine (a,d), polyethylene glycol (PEG) (b,e) and tap water (c,f) in six pigs

Cumulative output (irrigation approach and infusion regimen) (*Fig. 1*)

Data collected at 6 h provided strong evidence that the effect of irrigation route was influenced by the type of fluid used ($P < 0.001$). The mean cumulative output for antegrade *versus* retrograde irrigation was 1·99 *versus* 1·76 (95 per cent confidence interval (c.i.) 0·04–0·05) per cent ($P = 0.09$) for glycine, 2·31 *versus* 1·91 (c.i. 0·12–0·66) per cent ($P = 0.006$) for PEG and 0·79 *versus* 1·52 (c.i. 0·47–1·00) per cent ($P < 0.001$) for tap water. At 12 h there was again a highly significant interaction between irrigation approach and the

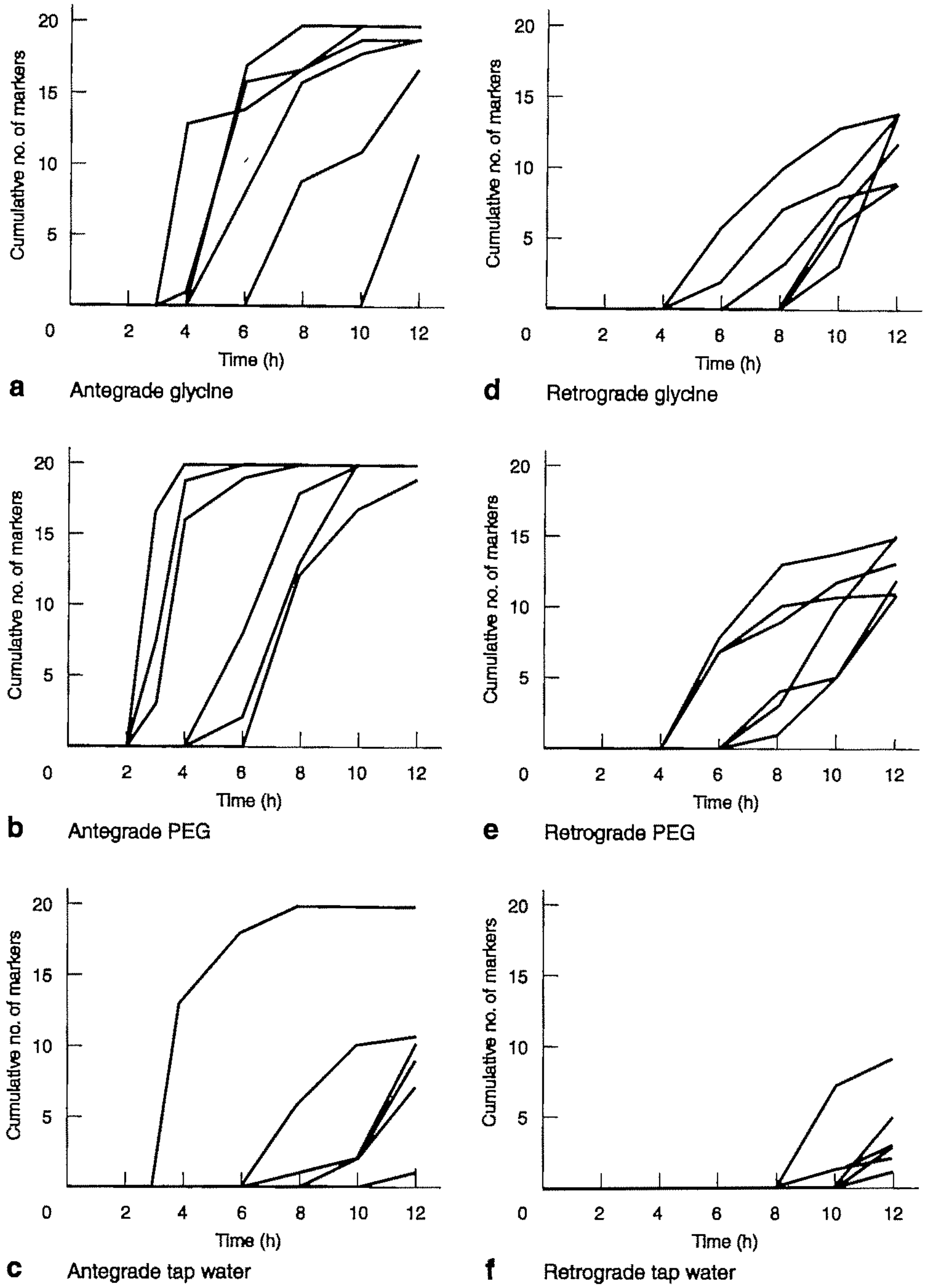
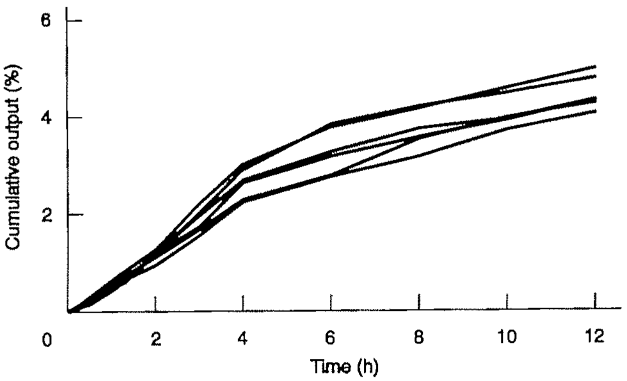


Fig. 2 Cumulative expelled markers for antegrade (**a**–**c**) and retrograde (**d**–**f**) irrigation with glycine (**a**,**d**), polyethylene glycol (PEG) (**b**,**e**) and tap water (**c**,**f**) in six pigs

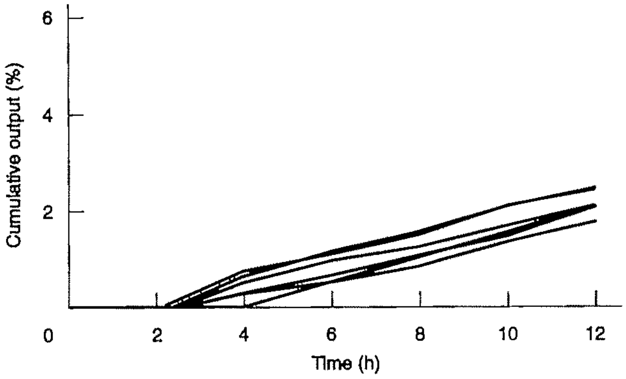
type of fluid used ($P < 0.005$). A similar pattern was observed for antegrade *versus* retrograde routes for each fluid regimen: 3·13 *versus* 2·87 (c.i. 0·02–0·54) per cent ($P = 0.07$) for glycine, 3·33 *versus* 3·01 (c.i. 0·04–0·60) per cent ($P = 0.03$) for PEG and 2·57 *versus* 2·88 (c.i. 0·03–0·59) per cent ($P = 0.03$) for tap water.

Cumulative expelled markers (irrigation approach and infusion regimen) (*Fig. 2*)

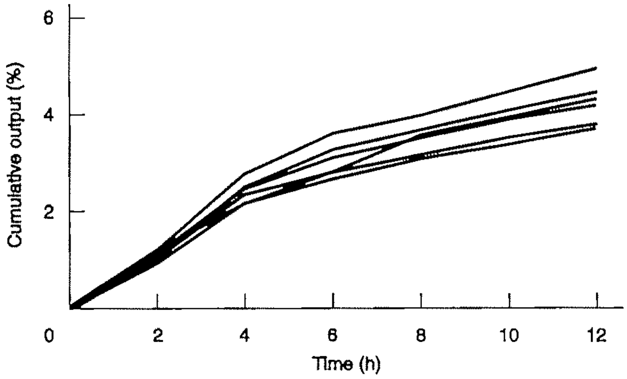
At 6 h more markers were expelled with antegrade than retrograde irrigation (7·89 *versus* 1·67 (c.i. 2·12–10·32); $P = 0.005$) but the difference between the three types of



a Bisacodyl



b Diltiazem



c GTN

Fig. 3 Cumulative faecal output for antegrade irrigation in six pigs treated with **a** bisacodyl, **b** diltiazem and **c** glyceryl trinitrate

Table 1 Difference in mean cumulative output over 12 h for each drug pair

	6h		12h	
	Mean difference (%)	P^*	Mean difference (%)	P^*
Bisacodyl *versus* diltiazem	2·44	< 0·001	2·35	< 0·001
Diltiazem *versus* GTN	−2·18	< 0·001	−2·08	< 0·001
Bisacodyl *versus* GTN	0·26	0·009	0·26	0·08

GTN, glyceryl trinitrate, *ANOVA

irrigation fluid was not significant ($P = 0·06$). At 12 h there was a significant difference between the mean CEM for the two routes (15·72 *versus* 9·56 (c.i. 3·98–8·34); $P < 0·001$) as well as for the three fluid regimens ($P < 0·001$). The mean CEM for glycine (14·83), PEG (16·33) and tap water (6·75) provided the following paired mean differences: −1·50 (c.i. −1·17–4·17) ($P = 0·26$) for glycine *versus* PEG, 8·08 (c.i. 5·41–10·75) ($P < 0·001$) for glycine *versus* tap water and 9·58 (c.i. 6·91–12·25) ($P < 0·001$) for PEG *versus* tap water.

Cumulative output (pharmacological agents) (*Fig. 3*)

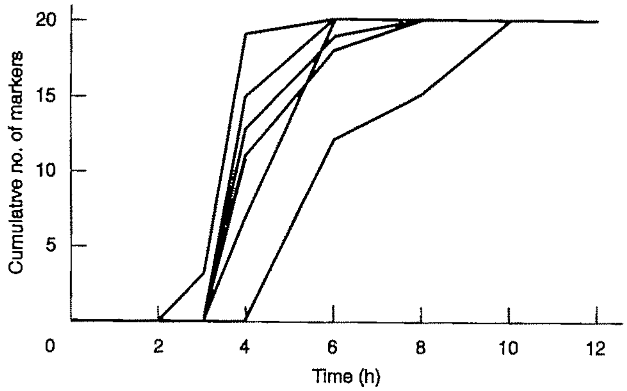
There was a highly significant difference between irrigation drug solutions at 6 h ($P < 0·001$). The highest mean cumulative output was for bisacodyl (3·24 per cent), then GTN (2·98 per cent) and the lowest value was for diltiazem (0·80 per cent). All pairwise differences between means were significant. A similar pattern emerged at 12 h ($P < 0·001$) and mean cumulative output values for bisacodyl, GTN and diltiazem were 4·44, 4·17 and 2·09 per cent respectively. However, on this occasion, the pairwise difference for bisacodyl and GTN was not significant (*Table 1*).

Cumulative expelled markers (pharmacological agents) (*Fig. 4*)

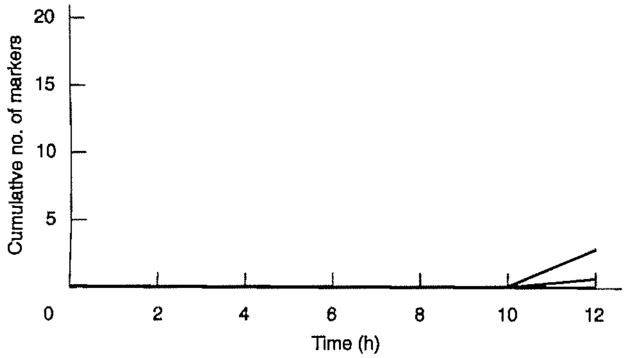
In terms of expelled markers, a significant difference was demonstrated between the three agents at 6 h ($P < 0·001$); the mean CEM was highest for bisacodyl (18·17), then GTN (12·17) while the lowest was for diltiazem (zero). As with cumulative output, all pairwise differences in mean CEM were significant. The mean CEM for bisacodyl, GTN and diltiazem were 20·00, 19·83 and 0·67 respectively at 12 h and their differences were highly significant ($P < 0·001$). As with the mean cumulative output at 12 h, the pairwise difference in mean CEM for bisacodyl and GTN was not significant (*Table 2*).

Discussion

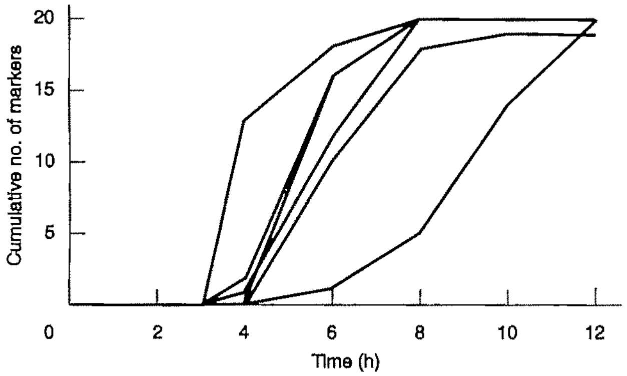
Colonic cleansing with water introduced via the caecum (antegrade) or colostomy (retrograde), is a useful but underutilized method of achieving faecal continence in selected conditions. Much success has been claimed with Malone's antegrade continence enema procedure for the



a Bisacodyl



b Diltiazem



c GTN

Fig. 4 Cumulative expelled markers for antegrade irrigation in six pigs treated with **a** bisacodyl, **b** diltiazem and **c** glyceryl trinitrate (GTN)

treatment of faecal incontinence and evacuatory disorders[11–14]. The resulting improvements in self-esteem and quality of life are comparable to those of colostomy management by irrigation[6–9]. However, both methods require considerable self motivation and are painstakingly time consuming.

Table 2 Difference in mean cumulative expelled markers over 12 h for each drug pair

	6 h		12 h	
	Mean difference	P*	Mean difference	P*
Bisacodyl *versus* diltiazem	18·17	<0·001	19·33	<0·001
Diltiazem *versus* GTN	−12·17	<0·001	−19·16	<0·001
Bisacodyl *versus* GTN	6·00	0·008	0·17	0·72

GTN, glyceryl trinitrate, *ANOVA

Large White (Landrace) pigs were selected for this study because of their close resemblance to humans in terms of anatomical structure, size and location of visceral organs. Since Hinton *et al.*[15] first described quantifying excretion of ingested radio-opaque markers, this technique has gained wide acceptance for measuring gut transit time. Similarly, in the above experiment, hourly collection and counting of expelled markers in the stoma bag provided a reasonably accurate assessment of colonic transit time. On the other hand, estimation of the amount of stool voided may have been a less reliable index of transit, as it was dependent on the amount of faeces in the colon, regardless of attempts to starve all animals for an equal length of time before irrigation. It was impossible to determine the level of discomfort to animals arising from each instillate into the colon, but the objective was to seek proof in principle that modification of technique might improve colostomy irrigation.

At 6 and 12 h, antegrade irrigation with PEG and 1·5 per cent glycine resulted in expulsion of more faecal effluent than did retrograde irrigation. This difference between the two approaches was significant for PEG but not for glycine. In the case of tap water, retrograde was significantly better than antegrade irrigation, possibly because of the viscosity of tap water causing frequent instant return into the stoma bag. This obviously contributed to the weight of faecal effluent measured. In all cases, the inability to predetermine accurately the amount of stool in the distal colon before irrigation might explain the disparity in the amount of faecal effluent measured.

For all three infusion regimens, significantly more markers were expelled with antegrade irrigation. PEG and 1·5 per cent glycine were more effective than tap water, possibly because of their diminished absorption by colonic mucosa, but the difference between these two regimens was not significant. One plausible explanation for the greater efficiency of the antegrade approach is that it is directed from the right to the left colon along with normal mass movement waves, ensuring efficient expulsion of stool. These findings support a recent study in a small number of colostomates indicating that antegrade irrigation through an appendicostomy is superior to the retrograde approach for improved stoma management and quality of life[16].

The mean number of markers expelled with GTN solution at 6 and 12 h was surprisingly greater than that with diltiazem and it was no different from the control at 12 h. Arguably, the bioavailability of the drug preparations and the different mechanism by which smooth muscle relaxation is induced might explain the contrasting effect of GTN and diltiazem solution. GTN is a potent nitric oxide donor, a neurotransmitter mediating relaxation of gastrointestinal smooth muscle[17]. However, contrary to expectation, enhanced colonic emptying of faecal effluent and markers was observed, as with the positive control. A possible link between the effect of GTN and bisacodyl may be provided by the suggestion that, at the cellular level, the laxative action of the latter is mediated by the release of nitric oxide from colonic epithelial, neural and smooth muscle cells[18].

Despite the limitations of this model, there are three important conclusions to be drawn from this study. First, antegrade irrigation of a colostomy is more efficient than the retrograde approach. There is thus a reasonable case to consider deliberate construction of an appendicostomy at the time of initial colostomy formation in patients interested in managing their future colostomy by irrigation. Second, PEG and 1·5 per cent glycine significantly enhance colonic emptying compared with tap water. There is thus proof in principle that manipulation of the irrigation fluid, or even the production of a colonoplegic solution, may improve the efficiency of colostomy irrigation in humans. Finally, colonic smooth muscle relaxation possibly via release of nitric oxide by GTN results in an improvement in evacuation similar to that achieved with bisacodyl. These findings show promise and may be clinically applicable in reducing the total time required to perform efficient colonic cleansing.

Acknowledgements

The authors are grateful to Mr Ken Harrison, Medicina, Berkshire, UK. A.O'B. is supported jointly by a grant from St Mark's Hospital/Northwick Park Institute for Medical Research and Dansac Ltd.

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Original article

Morbidity and functional outcome after double dynamic graciloplasty for anorectal reconstruction

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Background: After abdominoperineal resection (APR), anorectal reconstruction with dynamic graciloplasty has been proposed to avoid abdominal colostomy and improve quality of life. Graciloplasties involving one or two gracilis muscles with various configurations have been described. The aim of this study was to evaluate morbidity and functional results in a homogeneous series of patients undergoing double dynamic graciloplasty following APR for rectal cancer.

Patients and methods: From May 1995 to May 1998, 15 patients (ten men and five women; mean age 54 (range 39–77) years) underwent anorectal reconstruction with double dynamic graciloplasty after APR for low rectal carcinoma. All patients had preoperative radiotherapy (45 Gy), 11 with concomitant chemotherapy, eight had intraoperative radiotherapy (15 Gy) and ten received adjuvant chemotherapy for 6 months. The surgical procedure was performed in three stages: APR with coloperineal anastomosis and double graciloplasty (double muscle wrap); implantation of the stimulator 2 months later; and ileostomy closure after a training period.

Results: There was no operative death. At a mean of 28 (range 3–48) months of follow-up, there was no local recurrence; two patients had lung metastases. Early and late morbidity occurred in 11 patients, mainly related to the neosphincter (12 of 16 complications). The main complication was stenosis of the neosphincter ($n = 6$), which developed with electrical stimulation. Of 12 patients available for functional outcome, seven were continent, two were incontinent and three had an abdominal colostomy (two for incontinence, one for sepsis). Compared with patients without stenosis, patients with neosphincter stenosis required major reoperations (four *versus* zero) and had a poor outcome (two of six *versus* five of six with a good result).

Conclusion: The double dynamic graciloplasty is associated with a high risk of neosphincter stenosis, which may entail morbidity, reintervention and poor functional results. The stenosis is a heterogeneous feature of the neosphincter induced by asymmetrical traction of both gracilis muscles. It is suggested that single dynamic graciloplasty should be used for anorectal reconstruction after APR.

Presented to the 101st congress of the Association Française de Chirurgie in Paris, France, October 1999, and to the European Council of Coloproctology in Munich, Germany, October–November 1999
Paper accepted 19 January 2000
British Journal of Surgery 2000, 87, 909–913

Introduction

After abdominoperineal resection (APR), total anorectal reconstruction with coloperineal anastomosis and creation of a neosphincter has been proposed to avoid a permanent abdominal colostomy, with a view to improving quality of life[1–6]. Single dynamic (electrostimulated) graciloplasty has demonstrated its efficiency in faecal incontinence[7–9] and would appear to be the ideal option for restoring the anal sphincter after APR. Graciloplasties involving one or two gracilis muscles with various configurations (alpha, gamma, epsilon, split sling, posterior static wrap) have been described, but most series have included different techniques, and the best technique remains to be determined. This paper reports experience with a homogeneous series of double dynamic graciloplasties, analyses the failures and indicates that stenosis of the neosphincter may compromise outcome.

Patients and methods

Patients

From May 1995 to May 1998, 15 patients (ten men and five women with a mean age of 54 (range 39–77) years) underwent total anorectal reconstruction with double dynamic graciloplasty after APR for a low rectal adenocarcinoma. The mean lower edge of the tumour was located at 2·4 (range 0–5) cm from the anal verge. There were two T_2N_1, two T_3N_0, nine T_3N_1 and two T_4N_1 lesions (vaginal infiltration in two patients). No patient had distal metastases. All patients had preoperative radiotherapy (45 Gy), 11 with concomitant chemotherapy (5-fluorouracil). Eight patients included in a prospective clinical trial also had intraoperative radiotherapy (15 Gy). Postoperative chemotherapy (6 months of 5-fluorouracil and folinic acid) was given in ten patients. After treatment and according to the Astler–Coller classification, there were three stage B_1, nine stage B_2 and three stage C_2 tumours.

Operative procedure

The surgical technique, which has been published previously[10], was performed in three stages. In the first stage, APR with sigmoid colectomy was carried out, and the transverse and descending colon was mobilized. For patients with a fixed lesion on the vagina, a posterior colpectomy was performed, in one case with vaginal reconstruction using a colonoplasty[11]. The neosphincter consisted of a double graciloplasty as described by Geerdes *et al.*[4]. Both gracilis muscles without tendons were transposed around the distal colon through a small opening in the mesentery and fixed to each other. The double muscle wrap was performed without tension, usually admitting one or two fingers between the colon and the wrap. The objective was to obtain closure of the colon using electrostimulation of the gracilis muscles and not to create a tight neosphincter. Coloperineal anastomosis and a protecting loop ileostomy were then performed. In the second stage, 2 months later, a pulse generator (Itrel II 7424, Itrel III 3023; Medtronic, Boulogne-Billancourt, France) and two intramuscular electrodes (SP5566; Medtronic) were implanted. Three days later a 2-month training period was started[4], with intermittent stimulation with increased duty cycle (frequency 25 Hz, pulse width 210 s, amplitude 1·4 (range 0·8–1·8) V). In the final stage of the procedure, the ileostomy was closed when the neosphincter was functional without significant stenosis. A period of a few weeks (up to 3 months) of drug treatment was necessary to regularize bowel movements, and to attempt to coordinate bowel and neosphincter activities. Enemas were not used systematically.

The study was approved by the medical ethics committee. Informed consent was obtained from all patients.

Functional assessment

The patients were seen every 3 months during the year following stoma closure, then every 6 months. Functional results were classified according to the Williams continence scale[1]. Patients in stage I, II and III after APR (continent to solids or occasional incontinence to liquids) were considered to be continent.

Anal manometry was performed using a water-perfused catheter filled with three radially disposed side holes, located at a distance of 0·5 cm from each other (Armdofer ARM3; Medtronic-Synectics, Paris, France). The signals were analysed by a computer-assisted polygraph (Polygram 5·06C2; Medtronic-Synectics). The highest basal (unstimulated), squeeze (knees against each other) and electrostimulated pressures of the neosphincter were recorded. Results were expressed as median (range). Comparison of pressure data was performed using the Mann–Whitney test. $P < 0.05$ was considered significant.

Results

Deaths and recurrence

There was no operative death (30 days). Two patients died during the first year following APR. A 74-year-old patient presented with a colonic fistula which was treated by colostomy, and died from cachexia 3 months after APR. Another patient died 8 months after APR from pulmonary embolism.

Follow-up, performed every 6 months, included clinical examination, abdominal and pelvic computed tomography, chest radiography and measurement of carcinoembryonic antigen level. After a mean follow-up of 28 (range 3–48) months, there was no pelvic, perineal or liver metastasis. Two patients are alive with lung metastases.

Morbidity

Postoperative and late morbidity included 16 complications in 11 patients. Twelve were related to the neosphincter: colonic fistula (two patients), neosphincter stenosis (six), minor perineal abscess (two) and major perineal abscess with cellulitis (two). Complications not related to the neosphincter comprised colonic necrosis, occlusion, ileostomy prolapse and stimulator sepsis. The two colonic fistulas occurred at the beginning of the series and were due to excessive devascularization of the colon when creating the mesentery; treatment was by definitive colostomy. All other complications received conservative surgical treatment.

There was no postoperative perineal abscess and no delayed perineal healing, although preoperative radiochemotherapy was used. Perineal abscess occurred at the end of the training period, 10 days after continuous stimulation in one patient and during follow-up 8–15 days after increasing the stimulation amplitude in three.

Stenosis of the neosphincter was the most frequent complication observed in the present series. Stenosis usually developed during the training period and increased after continuous stimulation, making introduction of the anal manometry probe impossible in three patients. The stenosis was due to an heterogeneous aspect of the neosphincter which induced an S configuration of the colon (*Fig. 1*). Of six patients with a neosphincter stenosis, four major reoperations were necessary (neosphincter plasty in three, one with major abscess drainage; definitive colostomy for major pelvic abscess with destruction of the neosphincter in one). Only two minor reoperations were required for superficial abscess drainage among seven patients without stenosis.

Functional results

The median resting pressure of the neosphincter before implantation was 30 (range 15–57) cmH_2O. After a mean follow-up of 21 months after implantation, the median resting, squeeze and electrostimulated pressures were 33 (range 15–50), 200 (range 80–400) and 105 (range 70–170) cmH_2O respectively. There was no significant difference between the resting pressures before and after implantation (30 *versus* 33 cmH_2O; $P > 0{\cdot}05$), even though transformation of the gracilis muscles was achieved. There was a significant increase in neosphincter pressure with application of electrical stimulation (33 *versus* 105 cmH_2O; $P < 0{\cdot}0001$). The stimulation voltage at the date of end follow-up was 2·2 (range 1·6–2·8) V.

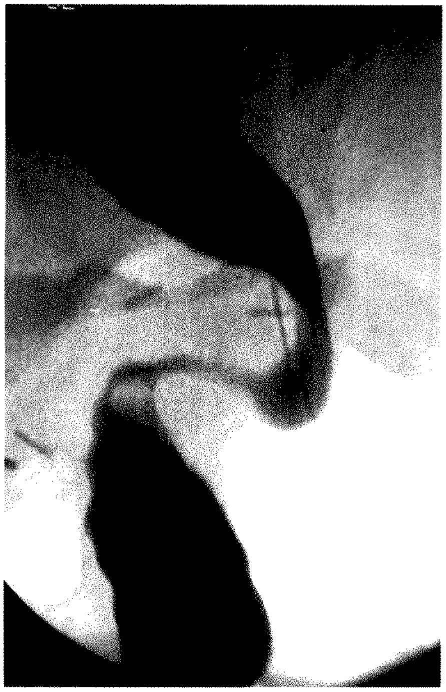

Fig. 1 Barium enema after double dynamic graciloplasty showing an S shape of the colon induced by neosphincter stenosis

Two patients had a colonic fistula, one of whom died, and one patient died early from intercurrent disease. Therefore, functional evaluation of patients who had closure of the ileostomy and follow-up of at least 1 year was available in 12 patients. Of these 12 patients, seven were continent (two with enemas), two were incontinent and three underwent an abdominal colostomy (two for incontinence, one for major pelvic sepsis). Long-term functional results were good in five of six patients without neosphincter stenosis but in only two of six with stenosis. Persistent incontinence in one patient without stenosis was due to intractable diarrhoea. The poor outcome in patients with stenosis was related to persistent stenosis with difficulties of evacuation and inability to use enemas ($n = 1$), low squeeze and electrostimulated pressures after plasty of the neosphincter for stenosis ($n = 2$), and major pelvic abscess with destruction of the neosphincter requiring iliac colostomy ($n = 1$). Evacuation difficulties were not present, especially in patients with spontaneous defaecation and without stenosis; however, half of these patients had fragmentation of stools and needed 30–90 min to obtain complete evacuation.

Discussion

In the present series, anorectal reconstruction with double dynamic graciloplasty allowed good functional outcome in seven of 12 evaluable patients. Failure was due to the morbidity related to the neosphincter, especially stenosis. There was no morbidity related to adjuvant treatment and no delayed perineal wound healing, suggesting that anorectal reconstruction with dynamic graciloplasty can be combined safely with preoperative radiotherapy and with preoperative or postoperative chemotherapy. No local recurrence was suspected with a mean follow-up of more than 2 years.

The reported cumulative morbidity rate after anorectal reconstruction with dynamic graciloplasty following APR is high, ranging from 40 to 90 per cent[3–6,10,12–15]. Postoperative morbidity usually decreases with the learning curve[8], but late morbidity can still occur, particularly following double dynamic graciloplasty. In the present series of double dynamic graciloplasties, late morbidity was related to neosphincter stenosis. The double muscle wrap is asymmetrical because one wrap is located inferiorly, whereas the other is superior (*Fig. 2a*). During the training period, the unfavourable feature of this configuration is increased by electrical stimulation, inducing an S shape of the colon (*Figs 1* and *2b*). During follow-up, increasing the stimulation amplitude to improve continence may result in colonic ischaemia with perineal abscess (*Fig. 2c*). Staging the procedure, by performing the coloperineal anastomosis first and the graciloplasty a few weeks later, may reduce the chance of ischaemia and sepsis. Stenosis after anorectal reconstruction is responsible for bad functional results because, as with coloanal or ileoanal pouch stenosis, incomplete evacuation of stool and subsequent faecal incontinence may occur. Furthermore, an S-shaped stenosis does not permit the use of enemas to improve functional results. In addition, repairing the neosphincter following a double muscle wrap did not allow creation of an efficient new neosphincter because the distal part of each gracilis muscle had been cut previously. These data suggest that double dynamic graciloplasty (double muscle wrap) is not the ideal neosphincter for anorectal reconstruction and should not be proposed for prospective trials. The presence of an S-shaped stenosis with inability to insert the manometry probe and the degradation of functional results with time[12], noted by Geerdes *et al.*[4] who first proposed this type of neosphincter, support these conclusions, although there was no comment about neosphincter morbidity in either paper[4,12].

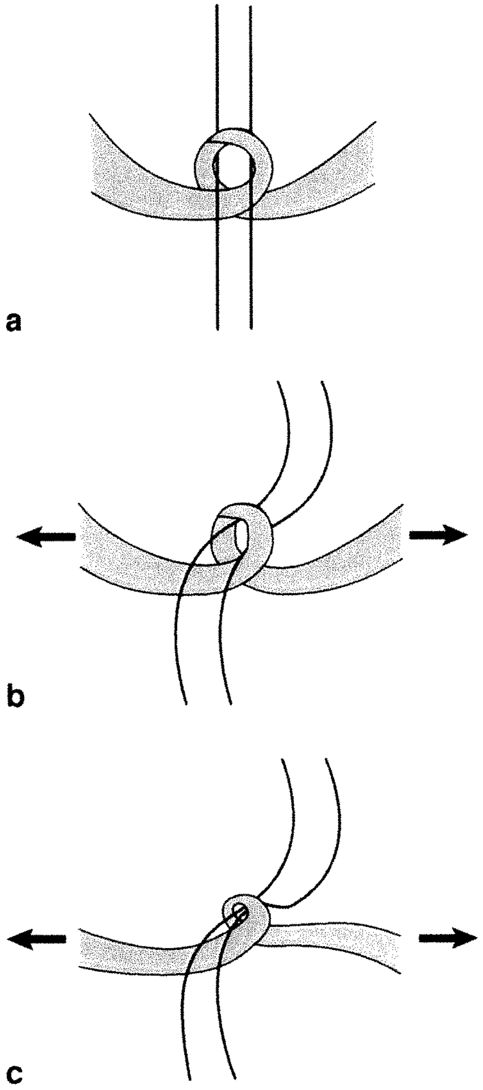

Fig. 2 Asymmetric traction of gracilis muscles after double dynamic graciloplasty.
a Before electrical stimulation.
b During training.
c After continuous stimulation

Cavina *et al.*[3,13] performed a double dynamic graciloplasty but only one gracilis muscle was used to create the neosphincter. One muscle was transposed around the neorectum and the tendon was sutured to the skin in an alpha-loop configuration. The second gracilis muscle was passed behind the colon in order to recreate the anorectal angle. Although there was a postoperative perineal infection rate of 22 per cent and an incidence of late complications related to the stimulator and leads of 13 per cent, they reported good continence in 22 of 26 evaluable patients[13]. In this series, the absence of neosphincter stenosis and the regular use of a water enema (mean 480 ml) may explain the good functional results. However, the role of the neosphincter and of the posterior sling, in terms of continence, remains to be determined, because the difference in resting and electrostimulated pressures of the neosphincter was very low (38 *versus* 55 mmHg)[13].

Williams *et al.*[1] used only one gracilis muscle. The neosphincter was carried out using a gamma, alpha or epsilon configuration. Because of technical failures, only six of 12 patients were evaluable[5]. In this series, the high morbidity rate, the lack of significant difference between the median basal pressure before stimulation and the functioning neosphincter pressure (30 *versus* 36 cmH$_2$O), and especially the various configurations used to create the neosphincter do not permit any conclusion about the optimal neosphincter for anorectal reconstruction. Likewise, in a series of nine patients described by Rouanet *et al.*[14] different kinds of neosphincter with either a straight or a pouch anastomosis were created, thus allowing no definitive conclusion. So far, the few patients in whom a pouch was tested in association with anorectal reconstruction did not have better functional results[5,12,14].

Rosen *et al.*[6] used a single electrostimulated graciloplasty, and they remodulated the alpha wrap into a split-sling configuration. A longitudinal incision was made in the muscle, and the distal part was pulled through. With the exception of their early experience, the absence of neosphincter-related morbidity and the good functional results (11 of 18 patients) suggest that this new configuration may be the best option for anorectal reconstruction. Indeed, the alpha-loop split sling has demonstrated its ability to create uniform high pressure in the neoanus[16]. Moreover, the use of a single gracilis muscle allows construction of a new functional neosphincter with the second one when major perineal sepsis occurs, which was indeed performed in this series[6].

In conclusion, the results of the present study showed that double dynamic graciloplasty was associated with a high rate of neosphincter stenosis that compromised functional outcome. This suggests that another kind of neosphincter should be used. The ideal neosphincter for anorectal reconstruction with dynamic graciloplasty should be symmetrical and homogeneous, allowing uniform compression; able to create a significantly higher pressure with electrical stimulation; associated with low morbidity and especially avoidance of stenosis; and performed with a single muscle to permit the use of the contralateral muscle if technical failure occurs.

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Original article

In-hospital delay in the diagnosis of breast cancer

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Background: There is evidence that delay in the diagnosis of breast cancer may prejudice survival. The aim of this study was to determine the incidence, time trends and causes of delay in a dedicated breast clinic.

Methods: The interval between first breast clinic visit and a definitive diagnosis was recorded in all patients with invasive breast cancer between 1988 and 1997. In all patients with a delay of 3 months or more, the case notes were reviewed for evidence of a triple assessment (clinical examination, imaging and needle biopsy). The principal cause of delay was identified.

Results: Of 1004 patients with invasive breast cancer, there was a delay in diagnosis of 3 months or more in 42 patients between 1988 and 1997, an incidence of 4·2 per cent. The median delay was 6 months and the median age at diagnosis was 53 (range 27–89) years. Triple assessment was undertaken in 30 patients; ten did not have a needle biopsy performed and three patients had no mammography. The principal cause of delay was: false-negative or inadequate fine-needle aspiration cytology (FNAC) in 19 patients, failure of follow-up in eight, clinical signs did not impress in five, FNAC not carried out in four, false-negative mammogram in three, failure of needle localization in two and one patient did not accept clinical advice. The annual incidence of delay in diagnosis did not change significantly over the 10-year interval.

Conclusion: Triple assessment is not sufficiently sensitive to detect every breast cancer and a small incidence of diagnostic delay is therefore inevitable with current techniques.

Paper accepted 24 January 2000

British Journal of Surgery 2000, 87, 914–919

Introduction

Delay in the diagnosis of breast cancer is an area of increasing litigation for medical practitioners, both in primary care and in hospital practice. The doctor who wishes to reassure an anxious patient must balance the risk of missing the diagnosis against creating unnecessary anxiety.

Whether delay in the diagnosis of breast cancer affects the outcome has been uncertain, but some studies have found evidence of reduced survival[1–3]. Others have failed to show any effect[4–6]. It is difficult to allow for the effect of lead-time bias when the earlier diagnosis of breast cancer may not alter the natural history of the disease, but appears to prolong survival. There may be other confounding variables so that more rapidly growing tumours with a poor prognosis may be clinically obvious to a doctor at the first consultation and lead to the paradoxical finding that earlier diagnosis makes the prognosis worse[7,8].

Nevertheless there is public expectation that earlier diagnosis and treatment improves outcome and in consequence delay in the diagnosis of breast cancer is increasingly accepted by the courts as a cause for recompense[9]. There is some consensus that a delay of more than 6 months is associated with a worse survival[10] and a recent systematic review of the literature that attempted to correct for lead-time bias suggested that a delay of more than 3 months may significantly reduce a patient's survival[11].

Previous experience from 1983 to 1988 showed that a delay in diagnosis of invasive cancer from the first breast clinic visit to definitive diagnosis of more than 50 days occurred in 7 per cent of patients, and more than 100 days in 2 per cent[12]. In the hospital setting the breast specialist is expected to carry out a triple assessment consisting of clinical examination, imaging and fine-needle aspiration cytology (FNAC) or core biopsy. The sensitivity of triple assessment that includes all patients with breast cancer who present to a breast unit is difficult to establish from the literature. In young women with a discrete mass, the sensitivity has been reported to be as low as 84 per cent[13] and as high as 100 per cent[14], although the latter rate would be difficult to match. In screen-detected cancers a sensitivity of 97·3 per cent has been reported[15], but this group is not representative of all patients. Furthermore, reported sensitivities are not always constrained by timeliness.

The aim of this study was to determine the incidence and causes of delay in the diagnosis of breast cancer from the time of secondary referral to a definitive diagnosis.

Patients and methods

All patients who presented with primary invasive breast cancer to the William Harvey Breast Clinic from January 1988 to December 1997 were considered. Data were recorded prospectively documenting the date of the first breast clinic visit with a sign or symptom in the same quadrant of the breast as the subsequent site of the proven tumour. The interval between the first breast clinic visit and a pathological diagnosis of breast cancer was recorded in all patients with invasive breast cancer. Where this interval was 3 months (84 days) or more, the case notes were reviewed. Where the general practitioner's referral letter was available and dated, the interval between this referral and the first clinic visit was also calculated. Documentation of the clinical diagnosis, the result of mammography and/or ultrasonographic examination, the findings on needle biopsy and the principal cause of delay were identified.

Where a core biopsy for histological examination was carried out at the first visit, this was usually in addition to FNAC. Occasionally a core biopsy was carried out in isolation where the lump was discrete, or latterly when a mass was obvious on ultrasonography. The term needle biopsy is used to signify either or both methods.

It was the unit's policy over the period of study to perform mammography on patients aged 35 years or over and to carry out FNAC in the presence of a palpable lump. Private patients were included in the database but patients with *in situ* carcinoma were excluded. In patients with a delay of 3 months or more the cytological assessment of all needle biopsies was reviewed by a single cytologist and all available mammograms were interspersed with contemporary negative films and re-read by a single breast radiologist without knowledge of the cases. Patients in whom delay appeared to be avoidable were identified separately. Patients referred through the National Health Service breast screening programme were not specifically excluded but none experienced a delay in diagnosis of 3 months.

Practice with regard to multidisciplinary meetings has changed over the 10-year interval so that cases with diagnostic difficulty or clinical interest have been discussed at a weekly meeting attended by the surgeon, pathologist, radiologist and clinical oncologist. Since 1996 the management of all breast cancers has been systematically discussed each week. At a separate meeting following a weekly one-stop breast clinic, all cases with diagnostic difficulty have been discussed by the clinician, breast radiologist and cytologist. However, the volume of work has prevented every single patient being discussed in detail.

Results

Some 1004 patients with invasive breast cancer were reviewed. There was a delay in diagnosis of 3 months or more in 46 patients who had invasive disease, but four patients were excluded from the study: in two patients no delay was evident on review of the notes and in two no records could be found. The incidence of delay in diagnosis of invasive breast cancer was 4·2 per cent; the annual incidence over the 10-year interval is shown in *Fig. 1*. The median delay in diagnosis for the 42 patients was 6 months (mean 13 (range 3–65) months) (*Table 1*). The extent of the delay varied as follows: from 3 to 6 months 18 (43 per cent), 6–12 months 7 (17 per cent), 1–2 years 9 (21 per cent) and over 2 years 8 (19 per cent). There was additional provider delay in responding to the general practitioner referral that amounted to a mean of 3 weeks and 4 days in the 36 patients with available data. The median age of the patients with diagnostic delay was 53 years (mean 56, range 27–89) years compared with a mean of 62 years in the total cohort of patients with breast cancer. The risk of delay in diagnosis for women aged under 50 years with invasive breast cancer was 6 per cent and for women of 50 years and over it was 3 per cent. A consultant breast surgeon was the senior clinical examiner at the first clinic visit in 37 of the 42 patients with diagnostic delay. Three patients were first seen by a specialist registrar and two by an experienced clinical assistant, but in no case was the junior trainee responsible for the delay. There were six private patients.

A triple assessment was carried out in 30 patients. Twelve patients did not undergo full triple assessment. Mammography was not performed in three patients, which was within protocol: two patients were aged less than 35 years and one patient had had a mammogram within the previous 12 months. This latter patient did not have a lump and therefore had no FNAC either. Neither aspiration cytology nor core biopsy was performed in ten patients, but six of these had no discrete lump. Two patients had a cyst aspirated but the fluid was not sent for cytological examination. In neither case was the cyst fluid blood-stained. One patient had an intracystic tumour and one had an adjacent carcinoma. In one patient there was a rather indefinite lump and a fine-needle aspirate was not obtained

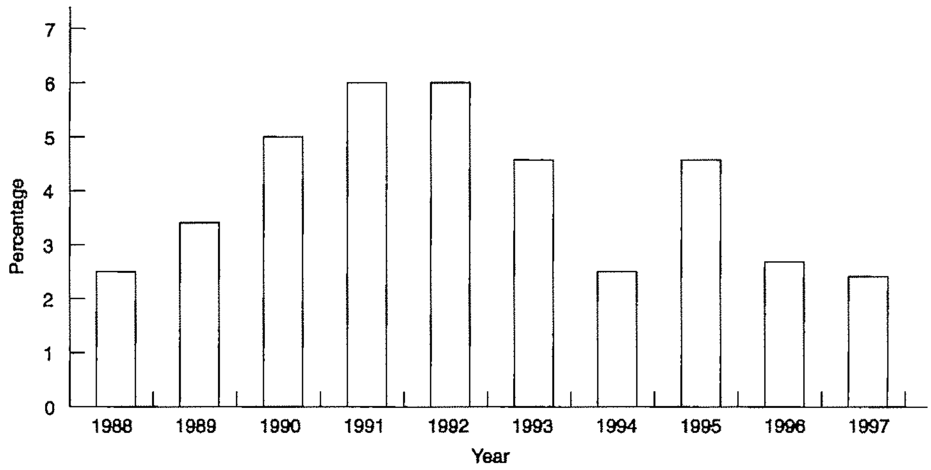

Fig. 1 Annual incidence of delay in diagnosis of invasive breast cancer of more than 3 months from 1988 to 1997

Table 1 Principal reason for delay in the diagnosis of breast cancer

	No. of patients (*n* = 42)	Mean delay (months)	Avoidable delay* (*n* = 18)
False-negative FNAC			
Sampling error (C2)	11		
Inadequate sample (C1)	3	6	5
Interpretation error (C4, C5)	5		
Failure of follow-up	8	10	5
Clinical signs not impressive	5	34	0
FNAC not done	4	17	4
False-negative mammogram	3	4	3
Needle localization failed	2	26	1
Patient refused advice	1		

Cytological classification: C1, inadequate; C2, benign; C4, suspicious; C5, malignant. FNAC, fine-needle aspiration cytology

because she was taking warfarin. One patient with a discrete lump did not have a needle biopsy carried out. Failure to carry out FNAC was identified as the principal cause of delayed diagnosis in four of these ten patients; the mean delay was 13 months.

The most common cause of delayed diagnosis was a false-negative or inadequate FNAC, which occurred in 19 patients (*Table 1*). Review of the FNAC findings by a cytopathologist found the original benign report (C2) to be false negative in five patients where the appearance was suspicious (C4) or frankly malignant (C5). In three patients the first fine-needle aspirate was inadequate (C1) but in 11 the aspirated material had been correctly interpreted as benign, with the presumption that the false-negative result was due to a sampling error by the clinician.

The clinical signs did not impress the examiner in three patients with nipple inversion and in two with breast pain, which led to delay in diagnosis. Two of the patients with nipple inversion had a blind FNAC taken from behind the nipple. All five patients were discharged from the clinic after the first visit and the reasons for re-presentation were an abnormality on screening mammography, nipple discharge, a palpable axillary node, nipple inversion and a lump. The mean age of these patients was 55 years.

Failure of follow-up occurred in eight patients (*Table 1*). Three did not attend the follow-up clinic, and in two patients a mammogram was reported as 'suspicious' but the typed report was filed and not acted upon. In one patient there was prolonged discussion with regard to a mammogram that caused a delay greater than 3 months. One patient should have had an appointment within 6 weeks, but it was arranged for 5 months, and in one patient follow-up was not arranged when it was clinically indicated. Three patients contributed to the delay in diagnosis by declining repeat FNAC where slight clinical suspicion persisted after an initial benign (C2) cytology. One of these was advised to have an excision biopsy but did not attend for surgery and returned with a locally advanced cancer 18 months later.

The mammograms were reviewed by a radiologist in a blind fashion and the original report was confirmed to be negative in 23 of the 26 patients for whom the mammograms were available. In three patients where delay was due to a false-negative mammogram the films were reported on review as suspicious, probably benign (R3).

In two patients needle localization biopsy failed to make the diagnosis of breast cancer at the first attempt, and led to a delay in diagnosis.

The method by which the definitive diagnosis was eventually established is shown in *Table 2*. Avoidable error

Table 2 Method of definitive diagnosis in patients with delay in the diagnosis of breast cancer

Method	No. of patients ($n = 41$*)
First FNAC	3
Second FNAC	7
Third FNAC	1
Fourth FNAC	2
First core biopsy	2
Second core biopsy	1
Ultrasonographically guided core biopsy	2
Excision biopsy	18
Needle localization biopsy	5

*One elderly patient returned with a clinically obvious carcinoma but refused repeat fine-needle aspiration cytology (FNAC)

leading to delay in the diagnosis of breast cancer proved a difficult value judgement, but in 18 patients this appeared to have been contributory (*Table 1*).

Fourteen of the 42 patients had been discharged from the breast clinic and were re-referred by the general practitioner. In eight patients the tumour was impalpable at the time of the original referral.

Discussion

Delay in the diagnosis of breast cancer may be taken from the onset of symptoms, which includes patient delay, or from presentation to primary care[16] which may be termed referral delay. However, these factors are outside the control of a specialist breast service and therefore this study concentrated on in-hospital or tertiary delay. It is on the basis of a pathological diagnosis that definitive treatment is planned and delay was therefore taken as the interval from the date of the first clinic visit to the definitive diagnosis of invasive breast cancer.

The administrative delay between the date of the general practitioner's referral letter and the first breast clinic visit was not taken into account but this amounted to a mean of 3 weeks and 4 days. In a separate study for the year 1996 where the referral delay for all invasive breast cancers was documented, the mean delay was 3 weeks and 1 day[17]. There is now a requirement in the UK that everyone with suspected breast cancer is seen by a specialist within 2 weeks of their general practitioner deciding that they need to be seen urgently and requesting an appointment[18].

The previously published incidence of delayed diagnosis of breast cancer of more than 100 days in all patients presenting to this breast clinic was 2·0 per cent[12], which is equivalent to the present rate of 4·2 per cent for the slightly shorter interval of 3 months. It is disappointing that the incidence of delay over the last 2 years of the study has not improved compared with the previous interval (1983–1988), and it is possible that further cases may become apparent that were first seen in 1997 when the minimum follow-up was only 12 months.

It is unusual for surgeons to discuss delay in diagnosis but Haagensen[19] did report 17 patients from a personal series of 1669 cases (1 per cent), although the criteria for timeliness were unstated. Data from the Yorkshire Cancer Registry (1976–1995)[20] show an overall provider delay of more than 90 days of 4 per cent. This rate includes the interval between the general practitioner's referral and first hospital visit but the in-hospital delay nearly doubled over the interval of study. In a recent small series[21] an in-hospital delay of 3 months or more was reported in 13 per cent.

Although improvements in clinical experience, imaging and cytopathology have occurred over the past 10 years, these have not been translated into a major reduction in the delay in diagnosis of breast cancer. The majority of patients were reviewed by a consultant breast surgeon at the initial visit so that the clinical experience of the examiner does not appear to be a major factor in the delay in diagnosis. Triple assessment is considered to be a satisfactory method of evaluating patients who present to a breast clinic but this was falsely negative in 30 of the patients with delayed diagnosis and it is clear that the assessment as currently practised is not sufficiently sensitive to detect all breast cancers.

Triple assessment may not be appropriate where there is no definitive sign to which fine-needle aspiration is amenable. Blind FNAC has never been advocated as a useful investigation since benign cytology in this situation may create a false sense of security. Where the clinical assessment is essentially negative, imaging alone has a lower sensitivity of 74–80 per cent[10,13,15].

Patients who present without clinical signs and normal findings on imaging are a difficult group in whom to prevent the delay in diagnosis of breast cancer. Where suspicion on clinical or mammographic grounds exists, benign cytological findings should not delay further investigation. There is some evidence that this may have been the cause of delay in up to 45 per cent of patients in the present study.

A sampling error that yielded an adequate sample of benign ductal cells (C2) was the commonest cause of a false-negative FNAC. The five patients in whom the cytology was misinterpreted as benign should be set against a breast cytology workload in excess of 1000 specimens per annum over 10 years. That represents one delay in diagnosis every 2 years being caused by a cytological misinterpretation (one in 2000 patients). The five cases were evenly spread over the 10 years and were not associated with the introduction of immediate reporting nor with any single cytologist. Over the same interval the sensitivity of FNAC for screen-detected cancers was well within the recommended limits[22]. In screen-detected cancers where the tumour is often impalpable, Yiangou *et al.*[15] found that 22 per cent of C2 lesions were found to be malignant after histological examination.

Repeated visits for patients where there is a low index of clinical suspicion on the history, examination or imaging would overload breast clinics to the point where delay in diagnosis may be caused by a backlog from general practice referral. The risk of administrative errors with follow-up appointments increases with the volume of referrals. The present initiative to reduce the number of consultations to a maximum of two[23] should improve administrative delay but may increase the risk of an occasional prolonged delay in diagnosis.

The definitive pathology in more than one third of the patients with delayed diagnosis was established by excision biopsy. When clinical suspicion was not confirmed by FNAC, a repeat aspirate at a second visit often failed to result in the pathological confirmation of malignancy. In these patients it was at the third or fourth visit, having exhausted other diagnostic options, that the clinician resorted to excision biopsy.

Younger patients have a higher rate of delay in diagnosis and tend to have a longer delays because they are more difficult to assess clinically[12,13,18] and mammography is less sensitive in dense breasts[24]. Lannin *et al.*[25] have reported a sensitivity of 64 per cent in women aged 40 years and 91 per cent in those of 75 years or over. Clinical practice has changed in the last 18 months of this study, with increasing use of ultrasonographically guided core biopsy, but it would be premature to suggest that this will reduce the incidence of delay. Ultrasonographic examination by a breast radiologist has been performed increasingly in younger patients in this unit since 1996 and current policy is to perform such imaging on all patients with localized clinical signs or symptoms.

The medicolegal implications of delayed diagnosis of breast cancer are considerable[11] and this may in part explain a general unwillingness to publish evidence of delay that may reflect badly on a unit or institution. However, most breast units will soon be equipped with a database that will enable ready calculation of the overall incidence of delayed diagnosis and this may become an important indicator of the quality of care. It is therefore possible to set a target for delay in diagnosis of 3 months or more for symptomatic invasive breast cancer; it is suggested that this should be less than 4 per cent. The increasing use of ultrasonographically guided core biopsy should enable this target to be achieved but this rate of delay in diagnosis would not be appropriate for screen-detected cancer or for ductal carcinoma *in situ* where the retrospective recognition of very early lesions may indicate a much longer delay[26].

This study does not address the all-important issue of causation: what is the effect of delay, its duration and the outcome in terms of life-years lost or loss of a chance of a cure? Whether a delay of 3 months or more shortens survival remains uncertain[27]. Liability is an important element of the legal process and, in the setting of a delay in diagnosis, this depends on the individual circumstances of the patient and the investigations carried out at the time. Practice is changing rapidly with the use of ultrasonography and multidisciplinary teams but it is essential that the clinician, radiologist and pathologist are able to show that they exercised a reasonable standard of care.

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Original article

Clinical relevance of sentinel lymph nodes outside the axilla in patients with breast cancer

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Background: Lymphatic mapping in patients with breast cancer can reveal sentinel lymph nodes that are not located at level I–II of the axilla. Little is known about the clinical relevance of these nodes.

Methods: Some 113 consecutive patients with clinical stage $T_{1-3}N_0M_0$ breast cancer were studied. Based on preoperative lymphoscintigraphy, sentinel node biopsy was performed guided by a γ probe and patent blue dye. All sentinel nodes that were visible on lymphoscintigraphy were sought. Pathological examination of the sentinel nodes included step-sections and staining with CAM 5·2. Axillary node dissection was performed regardless of sentinel lymph node status.

Results: Twenty-one (19 per cent) of 113 patients had sentinel lymph nodes outside level I–II of the axilla, mostly in the internal mammary chain. Twenty-two of the 30 sentinel nodes at these sites were harvested. Three patients had sentinel nodes only outside the axilla. Four other patients had metastases outside the axilla. This changed postoperative treatment in three patients. No postoperative complication occurred.

Conclusion: Sentinel lymph nodes outside level I–II of the axilla were present in 19 per cent of patients with breast cancer in this series. Biopsy of these nodes was technically demanding but was performed without additional morbidity. The clinical impact was limited; treatment changed in only 3 per cent.

Presented to the 52nd annual meeting of the Society of Surgical Oncology in Orlando, Florida, USA, March 1999 and the First International Congress on the Sentinel Node in Diagnosis and Treatment of Cancer in Amsterdam, The Netherlands, April 1999, and published in abstract form as *Eur J Nucl Med* 1999; 26(Suppl): S71

Paper accepted 29 December 1999

British Journal of Surgery 2000, 87, 920–925

Introduction

Axillary lymph node dissection is important for staging patients with breast cancer and for regional control. Approximately 60 per cent of patients have uninvolved axillary nodes and do not benefit from this procedure. Since there is no viable alternative, axillary clearance is considered routine practice in the treatment of early breast cancer[1,2]. Sentinel lymph node biopsy has been introduced recently and may be used to select patients for axillary treatment[3–6].

A sentinel lymph node is a node that receives direct lymphatic drainage from the primary tumour. The sentinel node will therefore be the first site of metastasis if lymphatic dissemination occurs[7]. Several studies have shown that the sentinel node can indeed be identified with blue dye[3], lymphoscintigraphy[8] and a γ probe[9,10], or with a combined technique[5]. If the axillary sentinel nodes are free of tumour, the chance of having axillary lymph node metastasis is probably so small that lymph node dissection can be omitted safely.

Although other investigators mention that sentinel nodes outside the axilla were visualized with lymphoscintigraphy in up to 38 per cent of patients, no report describes the systematic retrieval of such nodes[6,8,11–13]. Biopsy of sentinel nodes outside level I–II of the axilla could improve staging and thus improve the selection of patients for adjuvant radiotherapy and systemic therapy. This article describes the incidence of such nodes in patients with early stage breast cancer, the success of identification of these nodes, associated morbidity, and the impact on staging and treatment.

Patients and methods

From October 1996 to June 1998, all consecutive patients with an operable palpable breast tumour that appeared malignant on clinical examination, imaging (mammography, ultrasonography or both) and fine-needle aspiration cytology were asked to participate in a study validating the sentinel lymphadenectomy technique. Patients were not enrolled when an excision biopsy had been performed, when there was clinical evidence of axillary lymph node metastasis or when the patient was pregnant. The study was performed at two tertiary care hospitals in the Netherlands following the same protocol. This protocol was approved by the ethics committees of the participating centres and informed consent was obtained from all patients.

Sentinel node biopsy was performed as described in more detail elsewhere[14]. Lymphoscintigraphy was performed 1 day before surgery after intratumoral injection of 40–60 MBq ^{99m}Tc-labelled human albumen colloid (Nanocoll; Sorin Biomedica Diagnostics, Saluggia, Italy) in a volume of 0·2 ml. Dynamic and static images were obtained during 30 min after injection. Static images were repeated after 4 h. A hot spot was considered to represent a sentinel node if an afferent lymphatic vessel coming from the injection site was visualized. If no afferent vessels were seen, the surgeon was advised to search in both the axilla and internal mammary chain for the first nodes that had appeared on the lymphoscintigraphy images.

Immediately before surgery, 1·0 ml patent blue dye (Bleu Patenté V; Laboratoire Guerbet, Aulnay-sous-Bois, France) was injected into the tumour. Sentinel nodes were sought in the axilla through an incision at the border of the pectoralis major muscle in all patients by following blue-stained lymphatic vessels or by the γ probe (Neoprobe 1000/1500; Neoprobe, Dublin, Ohio, USA). Sites other than level I–II of the axilla were explored only when lymphoscintigraphy revealed hot spots there. All sentinel lymph nodes that would not be removed in a routine level I–II axillary clearance are referred to in the present paper as 'sentinel nodes outside the axilla'. Sentinel node biopsy was followed by level I–II (or III) axillary clearance regardless of sentinel lymph node status. Half of the patients were treated with mastectomy and the other half with breast-conserving surgery.

All sentinel nodes were completely embedded for microscopic evaluation and stained with haematoxylin and eosin, and immunohistochemistry for cytokeratin (CAM 5·2) at a minimum of at least three levels. Nodes up to 1 cm were embedded in two halves in one block, and larger nodes in parallel slices of 0·2 cm in more blocks. All blocks were cut at three levels at 100-μm intervals. All nodes removed during sentinel node biopsy which were considered to be non-sentinel nodes were processed in the same way. Additional nodes from the axillary dissection specimen were evaluated at one or two levels including immunohistochemical staining.

Results

Sentinel node biopsy was performed in 113 patients and the sentinel node was identified in 100. Twenty-one patients (19 per cent) had a sentinel node outside the axilla level I–II. Eighteen of these 21 patients had sentinel nodes both in the axilla and at another site. In the remaining three patients, all sentinel nodes were located outside the axilla (*Fig. 1*). Patient characteristics of each group are given in *Table 1*. Nine (13 per cent) of 68 patients with a tumour in the lateral quadrants of the breast had a sentinel node outside the axilla, compared with 12 of 45 of those with a tumour at a medial or central site.

The internal mammary chain was the most frequent location of sentinel nodes outside the axilla (17 patients). Three patients had sentinel nodes in the breast parenchyma. In two patients, one of the sentinel nodes was located in the infraclavicular fossa (axilla level III) and in two other patients a sentinel node was found deep in the interpectoral fossa (*Fig. 2*).

Intraoperative identification and sampling of sentinel nodes outside the axilla was found to be more difficult than for sentinel nodes in the axilla. Almost all axillary sentinel nodes were retrieved as identified on lymphoscintigraphy,

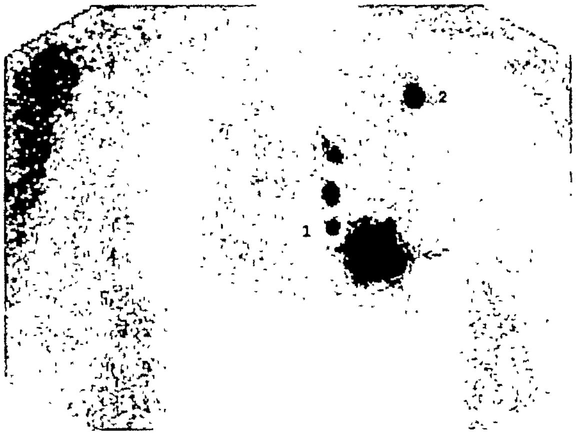

Fig. 1 Lymphoscintigraphy of a 44-year-old woman with a $T_1 N_0 M_0$ breast cancer in the upper inner quadrant of the left breast. Sentinel nodes were located in the internal mammary chain (1) and in between the pectoral muscles (2). No metastases were found in the sentinel nodes or in 16 additional axillary nodes

Table 1 Baseline characteristics of patients with sentinel lymph nodes in the axilla, outside the axilla, or both

		Site of sentinel nodes		
	All patients (n = 113)	Axilla only (n = 79)	Axilla and other site (n = 18)	Outside axilla only (n = 3)
Age (years)*	58 (33–89)	58 (33–89)	52 (34–79)	47 (44–49)
UICC clinical stage				
T_1N_0	55 (49)	38 (48)	9 (50)	3 (100)
T_2N_0	52 (46)	39 (49)	6 (33)	–
T_3N_0	6 (5)	2 (3)	3 (17)	–
Tumour location				
Upper outer quadrant	48 (42)	39 (49)	6 (33)	–
Lower outer quadrant	20 (18)	14 (18)	3 (17)	–
Upper inner quadrant	22 (19)	12 (15)	4 (22)	1 (33)
Lower inner quadrant	10 (9)	4 (5)	3 (17)	2 (67)
Central	13 (12)	10 (13)	2 (11)	–

*Values are mean (range); other values in parentheses are percentages. UICC, Union Internationale Contre Le Cancer

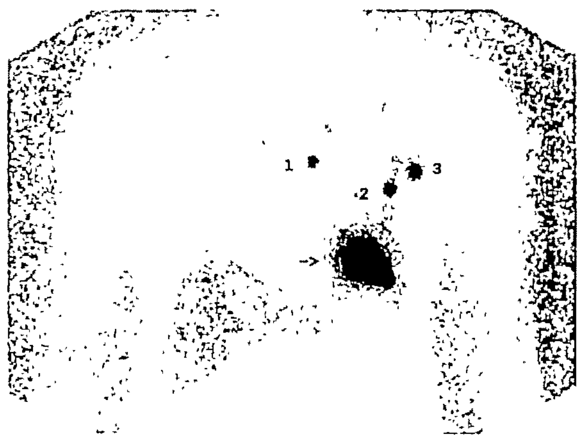

Fig. 2 Lymphoscintigraphy of a 71-year-old woman with a $T_1N_0M_0$ breast cancer in the upper inner quadrant of the left breast. Sentinel nodes were located in the internal mammary chain (1), deep in the interpectoral fossa (2) and in the axilla (3). Metastases were found in the first two sentinel nodes but not in the 18 axillary nodes, including the third sentinel node

but the retrieval rate of sentinel nodes outside the axilla was only 73 per cent (22 of 30 sentinel nodes). Several problems occurred with blue dye mapping outside the axilla. In the case of an internal mammary sentinel node, the blue lymphatic vessel could often not be followed into the intercostal space from the site at which it penetrated the pectoralis major muscle, and it was often damaged. Sometimes the blue vessel entered an intercostal space below the level of the sentinel node. Only 55 per cent of sentinel nodes (17 of 30) outside the axilla were found to be blue compared with 84 per cent in the axilla. Because the blue dye mapping was often not successful, γ probe detection was relatively important. The skin mark placed by the nuclear medicine physician to indicate the location was accurate and helpful. Intraoperative γ probe detection was, however, still more difficult than in the axilla. The location of sentinel nodes outside the axilla was often (in 14 of 21 patients) not established before operation with the γ probe; this occurred in only 27 per cent of axillary operations. The main reason for this was that the injection site was often close to the sentinel node. Most of the injected dose remained at the injection site, which caused a high background level of radioactivity. The level of radioactivity in the lymph node was low, only about 0·16 per cent of the injected dose (L. Jansen, unpublished data). In addition, the γ probe is relatively large and could not be manipulated freely between the ribs. In nine patients, the search for radioactive lymph nodes outside the axilla was resumed after excision of the primary site, which reduced the background level of radioactivity. Retrieval of (one of) the sentinel nodes was still not possible in six patients.

A third group of problems included general surgical difficulties. The overview of the area where the sentinel node was expected was limited through the narrow intercostal space. Sentinel nodes were sometimes located behind a rib. The sentinel nodes outside the axilla were small (1–5 mm), which made it difficult to recognize them as lymph nodes. Exploration of an intercostal space had to be performed cautiously to prevent damage to the pleura and the internal mammary artery.

The pleura was never opened when searching for an internal mammary node. In six patients, an extra incision in the skin had to be made to reach all sentinel nodes. No postoperative complications were seen from removal of sentinel nodes outside the axilla.

Table 2 Union Internationale Contre Le Cancer pathological node status by group

		Site of sentinel node		
	All patients ($n=113$)	Axilla only ($n=79$)	Axilla and other site ($n=18$)	Outside axilla only ($n=3$)
N_0	64 (57)	44 (56)	10 (56)	3 (100)
N_1	46 (41)	35 (44)	5 (28)	–
N_3	3 (3)	–	3 (17)	–

Values in parentheses are percentages

Eight of 21 patients with sentinel nodes outside the axilla had regional metastases (*Table 2*). Four of them had no metastases in the sentinel nodes outside the axilla. One patient had metastases in sentinel nodes in the interpectoral fossa and at level I of the axilla (stage pT_2N_1). Biopsy of the sentinel nodes outside the axilla therefore did not influence staging in these five patients. Three patients had tumour-positive sentinel nodes in the internal mammary chain. They were upstaged to pT_1N_3 (two patients) and pT_3N_3 (one patient) and received radiotherapy to the internal mammary chain. One of these three patients had no metastases in the axilla and also received adjuvant systemic treatment that would otherwise not have been given (*Fig. 2*).

Discussion

This study demonstrated that sentinel nodes were located outside level I–II of the axilla in a substantial number of patients with breast cancer (19 per cent). Retrieval of these lymph nodes was technically demanding, but the majority were harvested without additional morbidity. Systematic biopsy of these nodes altered staging in a few patients only (3 per cent).

The proportion of patients with tumour-positive lymph nodes outside the axilla only was small (one of 113), as was expected. In most patients with sentinel nodes outside the axilla, drainage occurred both to the axilla and to the internal mammary chain. Dissemination to internal mammary nodes is common: approximately 30 per cent in patients with primary operable breast cancer[15,16]. Urban and Baker[15] found metastases limited to the internal mammary chain in only 4 per cent of patients when performing radical extended mastectomy in the 1950s. Cody described Urban's last series of patients, selected for medial tumour location, and found that 11 per cent had metastases in the internal mammary nodes and not in the axilla[16]. In contrast, dissemination to nodes in between the pectoral muscles (Rotter nodes)[17] or directly to axillary nodes at level III is relatively rare[18,19]. The incidence of metastases outside the axilla only in the present series (one of 113) was lower than the 4 per cent found by Urban and Baker. An explanation for this difference could be that the latter population had more extensive disease and therefore more node-positive patients overall.

The impact on the indication for adjuvant systemic treatment was low for two reasons. First, the incidence of metastasis solely outside the axilla is low. Second, prognostic characteristics of the tumour itself determine the indications for adjuvant systemic treatment[20,21]. Consequently, most patients would have received adjuvant systemic treatment anyway. Metastasis in an internal mammary chain node is indeed an indication for systemic therapy because of the worse prognosis[16,22,23]. Half of the patients in this study had a T_1 tumour. They would be given the option to have adjuvant systemic treatment when the axilla was tumour negative. Twelve of these 55 patients (11 per cent of all patients) had sentinel nodes outside the axilla, and in one patient this was the only site of metastasis. Biopsy of sentinel nodes outside the axilla may be reserved for patients with a small tumour who would not be advised to have adjuvant systemic treatment when the sentinel node in the axilla was negative.

Whether the internal mammary chain nodes should be treated locally is controversial. Neither excision nor radiotherapy has convincingly been shown to improve the survival rate[24–26]. A limited survival benefit was seen in patients with axillary metastasis and a medial or central location of the primary cancer[16,23]. This is understandable because these patients have the greatest incidence of tumour-positive nodes in the internal mammary chain. Treatment of these nodes could theoretically prevent locoregional recurrence. Isolated recurrence in the internal mammary chain is a rare event[27]. Radiotherapy in the cardiac region may slightly increase the risk of myocardial infarction[28]. Although the benefit of radiotherapy to the internal mammary chain is not clearly shown, it is often given[29].

The impact of radiotherapy to the internal mammary chain on survival is the subject of an ongoing European Organization for Research and Treatment of Cancer trial (no. 22922). Patients are included when the tumour is in a medial location or when the axilla is tumour positive. These selection criteria are based on the results of radical extended mastectomy performed in the 1950s and 1960s[15]. Lymphatic mapping could be a more sensitive tool for selecting patients because it provides insight into the individual lymphatic drainage pattern[8,30]. The reliability of lymphoscintigraphy for indicating the first site of metastases has been established in many series of patients with melanoma or breast cancer[5,31,32]. When no drainage to internal mammary chain nodes is visualized or when an internal mammary sentinel node is free of tumour, the chance of having metastases at that site is probably less than a few per cent. Radiotherapy would then not be beneficial. The value of lymphatic mapping and sentinel node biopsy to select patients for adjuvant radiotherapy to the internal mammary chain should be investigated further.

Acknowledgements

The authors thank P. L. Jager and C. A. Hoefnagel, nuclear medicine physicians, J. L. Peterse, pathologist, and B. B. R. Kroon, surgical oncologist, for their contribution to the work presented in this paper; and H. S. Cody III, Memorial Sloan-Kettering Cancer Center, New York, USA, for comments on the manuscript.

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Original article

Transvenous sclerotherapy for huge oesophagogastric varices using open injection sclerotherapy

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Background: The optimum procedure for long-term management of oesophagogastric varices when endoscopic sclerotherapy or ligation fails is yet to be established. This report describes a new procedure for treating huge oesophagogastric varices by open injection sclerotherapy.

Methods: Twenty-three patients with huge oesophagogastric varices underwent laparotomy and devascularization of the upper stomach with splenectomy. The left gastric vein was catheterized for repeated injection of 5 per cent ethanolamine oleate during the postoperative period.

Results: In all patients, the varices were eradicated after a mean of 3 sessions of sclerotherapy. There were no deaths or major complications during the mean follow-up period of 41 months. Small recurring varices in two patients were treated successfully by endoscopic sclerotherapy and interventional radiology.

Conclusion: Open injection sclerotherapy is an effective and safe procedure for the treatment of huge oesophagogastric varices.

Paper accepted 10 January 2000

British Journal of Surgery 2000, 87, 926–930

Introduction

Endoscopic injection sclerotherapy and endoscopic variceal ligation are first-line treatments for both control of acute bleeding and prevention of rebleeding from oesophageal varices[1]. However, there is no agreement regarding long-term management of huge oesophageal varices or gastric varices that are difficult to treat at endoscopy. Sclerotherapy-resistant oesophageal varices may lead to the failure of sclerotherapy in 2–10 per cent of cases[2–4]. Despite promising results obtained with transjugular intrahepatic portosystemic shunting (TIPS)[5–7], patients with oesophageal varices in whom sclerotherapy fails and patients with gastric varices are still referred for surgical shunting, which has been suggested as the best form of treatment for bleeding oesophageal varices resistant to long-term sclerotherapy[8]. However, the high rate of postoperative encephalopathy after shunt operations is not acceptable in Japan because encephalopathy would be a serious impairment to the average patient with treated oesophagogastric varices, as most such patients return to jobs and other duties after operation. In Japan, the Sugiura procedure (paraoesophageal and gastric devascularization, oesophageal transection and splenectomy) and its modifications remain the operations of choice for patients with oesophagogastric varices in whom endoscopic sclerotherapy has failed[9].

In the search for less invasive treatments, Hassab's operation (oesophagogastric devascularization and splenectomy) has become popular[10–14]. Hassab's operation combined with endoscopic sclerotherapy constitutes the ideal therapy for varices of all types[10]. Nevertheless, this combination requires a prolonged period of time for eradicating the varices and may be associated with the well known complications of endoscopic sclerotherapy. The present study comprised a preliminary evaluation of the surgical results using a new approach to huge oesophagogastric varices. This approach employs trans-left gastric venous sclerotherapy following devascularization of the upper stomach and splenectomy, and is termed open injection sclerotherapy (OIS).

Patients and methods

Between July 1993 and June 1999, 23 patients with oesophagogastric varices underwent OIS with the approval of the ethics committee. Written informed consent was obtained from all patients for participation in this study of the new procedure. Patients' endoscopic findings were classified by means of previously reported criteria[15]; the oesophageal varices were either of a tumorous shape and huge size (F3) or of a nodular shape and moderate size (F2).

Preoperative coeliac and superior mesenteric arteriography was performed as described previously[3]. In all patients, the left gastric vein and oesophageal varices were clearly visible during the venous phase of arteriography and thus were classified as grade III. Nine patients had at least one episode of variceal bleeding; seven of them underwent endoscopic injection sclerotherapy with 5 per cent ethanolamine oleate to stop the bleeding before surgery, and two were treated by conservative means. The remaining 14 patients had large oesophageal varices with red colour signs, and were considered at risk for bleeding[15]. Patient characteristics are summarized in *Table 1*.

Operative procedure

The new procedure is illustrated schematically in *Fig. 1*. Following laparotomy, the upper half of the stomach was devascularized by ligating and dividing the left gastroepiploic and short gastric vessels. Splenectomy was performed routinely in all patients and was accompanied by ligation and division of all retrogastric venous collaterals. Following dissection of the lesser omentum, the left gastric vein was exposed and a 6-Fr catheter was inserted distally into the left gastric vein using a cut-off technique. The left gastric artery was doubly ligated with 2/0 braided silk thread, and divided. The left gastric vein was disconnected from the right gastric vein at the lesser curvature. Intraoperative left gastric venography was performed to confirm no connection of the left gastric vein to the portal or systemic circulation via the posterior gastric vein.

During the postoperative period, following injection of contrast medium (iopamidol) for visualization of residual varices, a sclerosant (5 per cent ethanolamine oleate mixed with iopamidol) was injected via the left gastric venous catheter. The injections were performed at 3–5-day intervals until complete obliteration of the varices was obtained. Oesophagogastric varices were considered obliterated when no variceal column was visible during endoscopy (F0) and no other vessels except the main trunk of the left gastric vein were revealed during radiological observation. The left gastric venous catheter was removed a few days after the last session of sclerotherapy. Removal of the catheter was not associated with any bleeding or other complications.

Table 1 Preoperative characteristics of 23 patients undergoing open injection sclerotherapy

Age (years)*	49 (11–69)
Sex ratio (M : F)	15 : 8
Causes of portal hypertension	
Liver cirrhosis	16
Idiopathic portal hypertension	6
Congenital hepatic fibrosis	1
Child grade	
A	16
B	6
C	1
ICG R15 (%)*	25·3 (2·6–55·4)

*Values are mean (range). ICG R15, indocyanine green retention rate at 15 min

Results

There were no intraoperative complications. The mean operating time was 256 (range 180–400) min (*Table 2*). The estimated intraoperative blood loss varied between 450 and 2400 (mean 1027) ml, but blood transfusion was required in only two patients.

The oesophagogastric varices were completely eradicated in all patients after a mean of 3 ethanolamine oleate injection sessions. The mean total volume of sclerosant required for eradication in each patient was 33 ml. Before sclerotherapy, left gastric venography usually revealed markedly enlarged and tortuous oesophagogastric collateral vessels, as seen in *Fig. 2a*. In this patient most of the oesophagogastric collateral vessels were obliterated after three sessions of sclerotherapy and only a partially obliterated main variceal channel remained visible during left gastric venography (*Fig. 2b*).

During the postoperative period, injection of the relatively large volume of sclerosant was complicated by

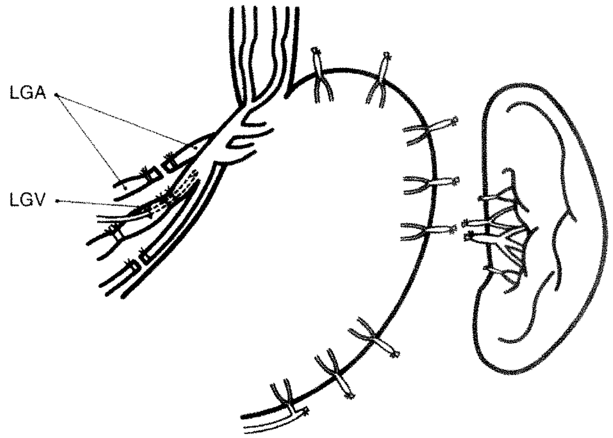

Fig. 1 Schematic representation of open injection sclerotherapy. Following devascularization of the upper half of the stomach and splenectomy, a 6-Fr catheter is inserted into the left gastric vein (LGV). LGA, left gastric artery

Table 2 Intraoperative characteristics and outcome of 23 patients undergoing open injection sclerotherapy

Operating time (min)*	256 (180–400)
Intraoperative blood loss (ml)*	1027 (450–2400)
Blood transfusion	2
Trans-left gastric venous sclerotherapy	
No. of sessions*	3 (2–5)
Total volume of sclerosant (ml)*	33 (13–58)
Postoperative complications	
ARDS	1
Pancreatitis	1
Follow-up (months)*	41 (12–71)
Small recurrent venous channels	2

*Values are mean (range). ARDS, adult respiratory distress syndrome (developed in patient with chronic obstructive lung disease)

adult respiratory distress syndrome in one patient with chronic obstructive lung disease. The postoperative period in another patient was complicated by development of mild pancreatitis. There were no deaths or major complications during the mean follow-up period of 41 months. In two patients small recurring oesophageal venous channels were noted at 3 and 6 months respectively. These varices were fed by a compensatorily enlarged right gastric artery and were eradicated successfully by radiological embolization of the right gastric artery and additional sessions of endoscopic injection sclerotherapy.

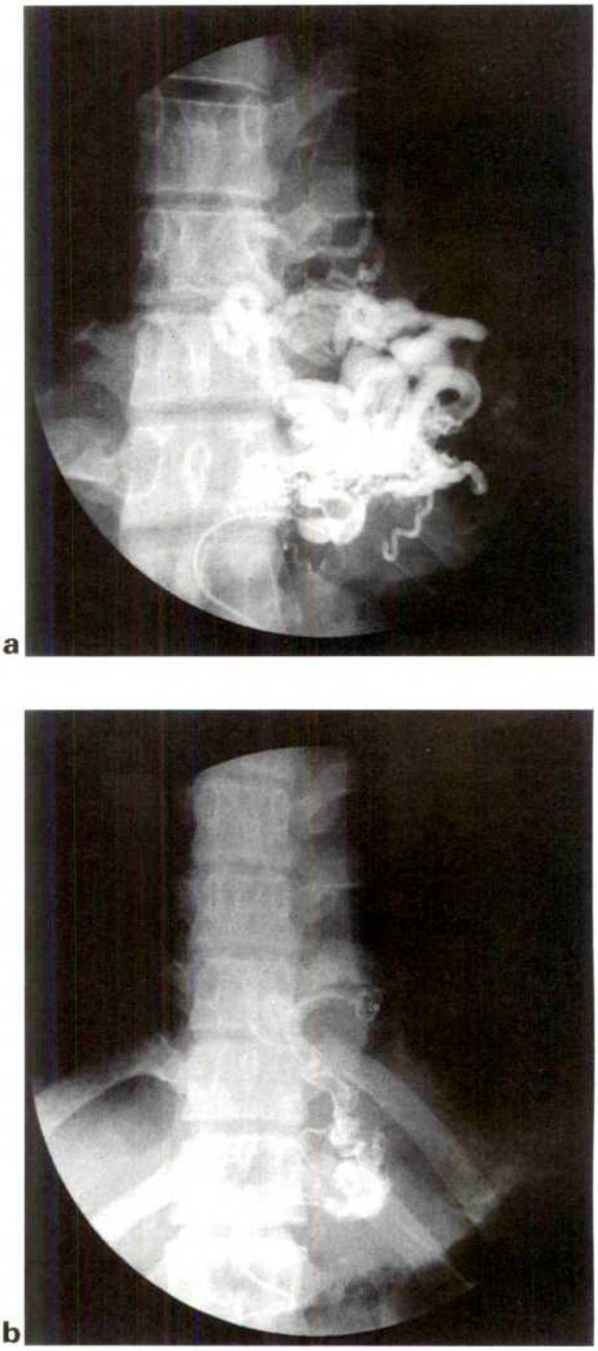

Fig. 2 **a** Postoperative left gastric venography before sclerotherapy. Note the markedly enlarged and tortuous oesophagogastric collateral vessels.
b After three sessions of sclerotherapy most of the oesophagogastric collateral vessels have been obliterated and only a partially obliterated main variceal channel remains visible

Discussion

Fourteen of the 23 patients had oesophageal varices that never bled; these patients were treated by OIS prophylactically. Although prophylactic treatments other than propranolol are not accepted in many countries, a meta-analysis of controlled randomized studies evaluating the efficacy of endoscopic injection sclerotherapy for primary prophylaxis of variceal bleeding showed that sclerotherapy prevents first variceal bleeding episodes and significantly reduces the mortality rate of patients with high-risk varices[16]. OIS is not recommended for primary prophylaxis of variceal bleeding in all patients with high-risk varices. OIS was performed in patients who might have benefited from prophylactic sclerotherapy and in whom endoscopic injection sclerotherapy might fail.

Repeated endoscopic injection sclerotherapy effectively eradicates oesophageal varices and, once the varices have been eradicated, significantly diminishes variceal bleeding[17–19]. However, some refractory oesophageal varices remain[2–4]. Although the definition of sclerotherapy-resistant oesophageal varices is controversial[2], it has been demonstrated that large varices require more injections for obliteration and often rebleed during treatment[20]. Recent studies have shown that enormously enlarged cephalad collateral vessels[3] or a large left gastric vein associated with a poorly developed extravariceal portosystemic shunt[4] are the characteristic portal venographic features of sclerotherapy-resistant varices. Although angiography is an invasive procedure and is not used routinely in all patients with oesophageal varices, it is most useful to predict whether the varices can be eradicated by endoscopic injection sclerotherapy[3]. In the present series, all patients had large oesophageal varices classified as grade III based on angiographic findings[3]. It has previously been shown that grade III oesophageal varices require more than 2 months' treatment and a mean of 8 sclerotherapy sessions to be eradicated[3]. These were the conditions under which the present authors consider that oesophageal varices in these patients might be resistant to repeated endoscopic injection sclerotherapy and are indicated for OIS. In addition, some patients also had large gastric varices that are difficult to eradicate and often rebleed after endoscopic injection sclerotherapy[21].

The optimum long-term treatment for sclerotherapy-resistant oesophagogastric varices is yet to be established. A recent meta-analysis of randomized controlled trials comparing TIPS and endoscopic treatments for the prevention of recurrent variceal bleeding has shown that TIPS markedly reduces the risk of bleeding but has a high rate of dysfunction (55 per cent) and increases the risk of encephalopathy without affecting the survival rate[5]. Therefore, it was concluded that TIPS may not be the best first-choice therapy for prevention of recurrent variceal bleeding. An increased risk of encephalopathy and high rates of shunt dysfunction associated with TIPS may also limit its use for the long-term management of sclerotherapy-resistant oesophageal varices. Moreover, fundic gastric varices often fail to disappear with TIPS[7]. Endoscopic variceal ligation, an alternative endoscopic technique, is now considered a treatment of choice in the management of variceal bleeding[22]. However, the recurrence rate after endoscopic variceal ligation during long-term follow-up remains high, and its efficacy for sclerotherapy-resistant varices is still unknown.

Surgery remains the most reliable treatment for long-term management of oesophagogastric varices. Surgical portosystemic shunts are very effective but are associated with a high rate of encephalopathy[23]. In the present series most patients had posthepatitis liver cirrhosis with relatively good liver function or idiopathic portal hypertension. For patients with the potential to continue an active life and employment after treatment of varices, treatment-induced encephalopathy is generally considered to be unacceptable. Currently, the Sugiura procedure and its modifications are often used when non-surgical treatments fail[9,23]. However, these procedures are invasive and require oesophageal transection, which is an important factor contributing to the overall mortality and morbidity rates[24].

Giant bar-type oesophageal varices not eradicated by repeated endoscopic injection sclerotherapy were found to be well controlled by the Hassab procedure[14]. Recently, a laparoscopic adaptation of Hassab's operation has been applied to gastric varices[11] and to sclerotherapy-resistant oesophageal varices[12] with good results. Study of the venous anatomy of the lower oesophagus in portal hypertension has demonstrated major intramural communications between the oesophageal and gastric deep intrinsic veins[25]. Hassab's procedure is effective for extramural connections; however, for the intramural connections, sclerotherapy is also necessary[26]. Hassab's operation and intraoperative endoscopic injection sclerotherapy in combination have been suggested for advanced oesophagogastric varices, but possible excessive vessel damage and associated post-operative bleeding may limit the use of these procedures in combination[13]. For successful endoscopic injection sclerotherapy, an adequate volume of sclerosant must be injected accurately into the varices so as to allow the sclerosant to damage the endothelium of vessels for further obliteration[17]. The large size and high blood flow rate of varices may hinder their complete obliteration by endoscopic injection sclerotherapy. OIS allows for easy and precise intravariceal injection of sclerosant via the catheter placed in the left gastric vein. Moreover, gastric devascularization diminishes variceal blood flow, thus establishing favourable conditions for variceal obliteration by the sclerosant. In addition, OIS facilitates eradication of varices without the well known complications of endoscopic injection sclerotherapy, such as bleeding from an oesophageal ulcer or oesophageal stenosis.

The long-term results of OIS are still unknown. In this study, small recurrent venous channels were noted in two of the 23 patients. The reason for the recurrence was considered to be incomplete gastric devascularization and subsequent development of new collaterals. Careful and complete devascularization of the upper stomach may help to prevent the recurrence of varices in patients undergoing OIS. It must be shown in comparative studies whether OIS is advantageous compared with Hassab's operation for the long-term management of sclerotherapy-resistant oesophageal varices. However, these preliminary results suggest that OIS is an effective and safe procedure in the treatment of huge oesophagogastric varices.

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Surgical Infection Society of Europe Abstracts

The following abstracts and posters were presented to the joint meeting of the Surgical Infection Society of Europe and the European Shock Society held in Nijmegen, The Netherlands on 25–27 May 2000

Improved survival of tumour necrosis factor-deficient mice during zymosan-induced multiple organ dysfunction syndrome

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Background: Tumour necrosis factor (TNF) is believed to be a crucial mediator in systemic inflammation and the multiple organ dysfunction syndrome (MODS). Previous studies in this laboratory with a murine model have shown that interventions directed at TNF could mitigate the symptoms of zymosan-induced MODS. The present study aimed to investigate the course of MODS in the absence of TNF.
Methods: Twenty-four TNF/LT-knockout (–/–) mice and 25 wild-type (+/+) mice received an intraperitoneal dose of lipopolysaccharide 40 mg, followed by zymosan 1 mg per g body-weight 6 days later (day 0). Survival, body-weight and body temperature were monitored. At day 22 ten –/– mice and five +/+ mice were killed, and organs were collected and weighed. The remaining animals were followed until day 48, when all were killed and their organs harvested for histological examination.
Results: In all animals zymosan induced an acute sterile peritonitis phase followed by an apparent recovery. From day 8 onwards the +/+ mice entered a third, MODS-like, phase, characterized by loss of body-weight, decreased body temperature and significant mortality rate. At day 22, survival in the –/– mice was 92 per cent, which was significantly ($P<0{\cdot}05$) higher than that in the +/+ mice (60 per cent). In addition, mean body temperature and mean relative body-weight (*versus* weight at day 0) were 33·3°C and 84 per cent respectively in the +/+ mice. Data for the –/– mice were 35·9°C and 100 per cent respectively ($P<0{\cdot}05$). However, at this time point, both the +/+ mice and the –/– mice showed significant and similar organ damage, indicated by an increase in absolute and relative (*versus* body-weight) weight of lung, spleen and liver (the last organ only in the –/– mice). Moreover, at day 48 histopathological examination of liver, lungs, spleen and kidneys from the surviving animals showed a similar degree of microscopic damage in both the –/– and +/+ mice.
Conclusion: TNF-deficient mice exhibit significantly improved survival during zymosan-induced MODS and their clinical condition appears to be better than that of wild-type animals. However, surviving animals from both groups eventually display a similar degree of organ damage. Thus, in this murine model, the absence of TNF does not completely protect against MODS.

Bacterial lipoprotein delays neutrophil apoptosis via a CD14-independent pathway

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Background: Lipopolysaccharide (LPS) is considered the most potent exogenous mediator of the systemic inflammatory response syndrome (SIRS) which results, in part, from delayed neutrophil (PMN) apoptosis. The effects of another ubiquitous bacterial component, bacterial lipoprotein (BLP), the most abundant protein in the cell wall of all bacteria, on PMN apoptosis are unknown. The potential role of BLP in the regulation of PMN apoptosis was investigated and these effects were compared with those of LPS.
Methods: PMNs from healthy volunteers were isolated and exposed to identical concentrations of LPS and BLP in the presence or absence of recombinant antihuman CD14 monoclonal antibody. PMN apoptosis was assessed 6 hourly using Annexin V–propidium iodide staining and confirmed on cell morphology. PNM activation was assessed flow cytometrically using expression of functional markers CD11b and CD18.

Results:

	PMN apoptosis (%)						
		BLP (μg)			LPS (μg)		
	Control	10	100	1000	10	100	1000
6 h	11	8*	7*	6*	7*	6*	7*
12 h	24	12*	10*	8*	9*	8*	9*
18 h	41	26*	17*	18*	15*	16*	15*
24 h	53	36*	31*	31*	27*	27*	28*

Values are mean(s.d.). $^*P<0{\cdot}0005$ *versus* control (analysis of variance)

BLP significantly delayed PMN apoptosis and upregulated PMN adhesion receptor expression compared with control values. The effects seen were markedly similar to those of LPS.
Conclusion: BLP is capable of upregulating PMN adhesion receptor expression and delaying PMN apoptosis in a time- and

dose-dependent manner independent of CD14. The potency, and the effects mediated by, BLP are very similar to those of LPS. This identifies BLP as a putative mediator of SIRS and demands that due attention be paid to other bacterial products in the investigation and treatment of septic states.

Effect of bacteria and antibiotic treatment on whole blood-mediated endothelial permeability *in vitro*

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Background: During Gram-negative sepsis bacterial endotoxin or lipopolysaccharide (LPS) may activate and damage endothelial cells resulting in systemic vascular leakage. Antibiotic treatment of Gram-negative bacteria results in significant release of LPS, inducing production of cytokines by leucocytes *in vitro*. The biological relevance of this finding is not well understood. A whole blood assay and cultured endothelial monolayers have been used to evaluate the effect of antibiotic treatment of bacteria on endothelial permeability.
Methods: Heat-inactivated (HI) *Escherichia coli* (ATCC 25922) was treated with either cefuroxime (CXM), imipenem–cilastin (IPM) or polymyxin B (poly B). The cultures were incubated with heparinized whole blood from healthy donors in a final concentration of 10^5 colony-forming units ml^{-1} and incubated at 37°C for 24 h. Plasma was then collected and added to human umbilical vein endothelial cell monolayers cultured on semi-permeable Transwell COL membranes. The permeability of the monolayers was determined using fluorescein isothiocyanate-labelled (FITC) albumin and rhodamine-β-isothiocyanate-labelled (RITC) dextran. The production of interleukin (IL) 1β, IL-6, IL-1ra and tumour necrosis factor (TNF) α in whole blood was measured using radioimmunoassay.
Results: In whole blood, HI bacteria alone induced the production of IL-1β, IL-6, IL-1ra and TNF-α. CXM treatment of HI *E. coli* before incubation in blood induced significantly more IL-1β, TNF-α and IL-6 than the HI control, while poly B treatment induced less cytokine production. IPM did not significantly alter the production of cytokines. In the permeability assay, whole blood treated with HI bacteria alone induced a permeability increase of 2·3 times control monolayer permeability ($P < 0{\cdot}05$). While CXM or IPM treatment resulted in a significant further enhancement of the permeability, there was no significant difference between these antibiotic treatments (permeability increase 2·9 and 2·8 times the control respectively). In contrast, treatment with poly B almost completely abrogated the permeability effect of HI bacteria (1·1 times control; $P > 0{\cdot}05$).
Conclusion: Since neutralization of LPS by poly B reduces the *E. coli*-induced production of cytokines in whole blood and prevents increased permeability, free LPS may be the driving force of cytokine-mediated endothelial permeability. Treatment of bacteria with CXM or IPM induces a significantly different cytokine production in whole blood. However, in both cases the resulting plasma leads to a similar increase in permeability. Thus, the fact that individual antibiotics can release different amounts of LPS may be irrelevant to endothelial permeability.

Bacterial lipoprotein induces tolerance in human THP-1 monocytes with reduced tumour necrosis factor α production via a CD14-independent pathway

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Background: Endotoxin (lipopolysaccharide; LPS) tolerance is characterized by diminished production of tumour necrosis factor (TNF) α during prolonged exposure to LPS, and therefore represents an essential control mechanism during sepsis. However, it is unknown whether bacterial lipoprotein (BLP), another major component of bacterial walls, can cause tolerance. This study sought to determine whether BLP pretreatment can induce tolerance in human THP-1 monocytes.
Methods: Human THP-1 monocytic cells were pretreated with culture medium alone and medium containing LPS 10 ng ml^{-1} or BLP 10 ng ml^{-1} for 24 h. Cells were further stimulated with high doses (0·1–1 mg ml^{-1}) of LPS or BLP for 6 h. TNF-α levels were determined by enzyme-linked immunosorbent assay. CD14 receptor expression on THP-1 monocytes was assessed by flow cytometry.
Results:

	TNF-α (pg ml^{-1})			
	LPS post-treatment (mg ml^{-1})		BLP post-treatment (mg ml^{-1})	
Pretreatment	0·1	1·0	0·1	1·0
Medium	501(147)	1318(463)	3041(637)*	2876(644)*
LPS	35(5)†	74(28)†	350(86)*†	239(5)*†
BLP	30(8)†	40(10)†	41(9)†	37(7)†

Values are mean(s.d.) ($n = 4$). *$P < 0{\cdot}05$ *versus* LPS stimulation, †$P < 0{\cdot}05$ *versus* medium pretreatment (analysis of variance)

When THP-1 cells were incubated with culture medium, BLP stimulation resulted in much higher TNF-α levels than LPS stimulation ($P < 0{\cdot}05$). Following LPS pretreatment, LPS stimulation-induced TNF-α production was significantly attenuated, whereas BLP stimulation still produced a small amount of TNF-α. However, BLP pretreatment prevented both LPS and BLP stimulation-induced TNF-α production from THP-1 cells. FACScan analysis revealed that THP-1 monocytes do not express CD14 receptor.
Conclusion: These results demonstrate that BLP has a more potent effect than LPS on THP-1 monocyte TNF-α production. Furthermore, BLP pretreatment is capable of inducing

both BLP as well as LPS tolerance via a CD14-independent pathway, indicating a unique ability to cause cross-tolerance.

Nitric oxide synthase-independent pathway(s) of nitric oxide formation after intestinal ischaemia–reperfusion

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Background: Recent evidence suggests that nitric oxide produced in the gastrointestinal tract, in concert with other vasoactive mediators, plays an essential role in the regulation of splanchnic circulation.
Methods: To determine the sites and pathways of nitric oxide formation, electron paramagnetic resonance spectroscopy and the nitric oxide trap diethyldithiocarbamate-Fe were used to detect directly nitric oxide formed in intestine, liver and lungs of rats subjected to local intestinal ischaemia–reperfusion (I/R), in the presence or absence of nitric oxide donors or inhibitors. In addition, the role of nitric oxide in control of the gastrointestinal circulation was determined by means of a coloured microsphere technique employing N-(G)-Monomethyl-L-arginine (L-NMMA) in rats subjected to haemorrhagic shock followed by resuscitation.
Results: In contrast to remote organs lung and liver (no change), intestinal I/R resulted in an increase in nitric oxide formation in intestinal tissues. Administration of the non-specific nitric oxide inhibitor L-NMMA caused a decrease in I/R-independent basal nitric oxide levels in lung and liver but did not influence the I/R-induced increase in nitric oxide formation in intestinal tissues. In support of this, reverse transcriptase–polymerase chain reaction analyses showed inducible nitric oxide synthase (NOS) expression in the lung but not in intestinal tissues. In the microsphere experiment, a moderate and therapeutic dose of L-NMMA administered after the completion of resuscitation, which improved haemodynamic conditions and outcome, did not alter the intestinal circulation.
Conclusion: The data suggest that the early-phase I/R-induced nitric oxide formation in ischaemic intestinal tissue is probably NOS independent, while nitric oxide formation in normoxic remote tissues is partially NOS dependent. In addition, the authors' nitric oxide-related therapeutic approaches reveal that only the regulation of nitric oxide (e.g. nitric oxide supplementation during resuscitation or reperfusion and/or nitric oxide inhibition or modulation after resuscitation) may protect against hypovolaemic insults.

Mild endotoxaemia during low arginine plasma levels reduces blood flow to the small intestine

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Background: Arginine is the sole precursor in the generation of the vasodilating agent nitric oxide. Plasma levels of arginine are low in situations associated with endotoxaemia such as major trauma, sepsis and experimental obstructive jaundice. The aim of the study was to evaluate haemodynamics at low arginine plasma levels during low-grade endotoxaemia.
Methods: Rats were assigned randomly to receive (at $t = 0$ min) an intravenous infusion of 1·5 ml sodium chloride 0·9 per cent (SAL, $n = 12$) or 1·5 ml arginase solution (3200 units) (ASE, $n = 17$) over 20 min. After the SAL or ASE infusion, rats were randomly assigned to receive an intravenous endotoxin (lipopolysaccharide; LPS; 150 $\mu g\,kg^{-1}$ in 1·0 ml 0·9 per cent sodium chloride) challenge (ASE-LPS, $n = 10$ and SAL-LPS, $n = 6$) or a control infusion of 1·0 ml 0·9 per cent sodium chloride (ASE-SAL, $n = 7$ and SAL-SAL, $n = 6$) at $t = 30$ min. Organ blood flow was measured at $t = 270$ min, using radiolabelled microspheres.
Results: At 270 min arginine plasma levels were lower in the ASE-treated rats (ASE-SAL *versus* SAL-SAL and ASE-LPS *versus* SAL-LPS, both $P < 0.005$). Cardiac output, mean arterial pressure and therefore total peripheral resistance were similar for all groups. In the LPS-treated animals (SAL-LPS and ASE-LPS) cardiac output was maintained by a higher heart rate compensating for the lower stroke volume. Organ blood flow to the small intestine and splanchnic blood flow were lower in the ASE-LPS-treated rats (both $P < 0.05$ compared with other groups). Total liver blood flow was similar for all groups; the lower splanchnic blood flow was compensated for by a higher hepatic arterial blood flow.
Conclusion: This study shows that low plasma levels of arginine do not influence organ blood flow while, during low-grade endotoxaemia, low arginine plasma levels result in reduced blood flow to the small intestine.

Renal arginine synthesis is impaired after experimental ischaemia–reperfusion

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Background: Endogenous arginine synthesis is important for maintaining normal plasma levels of arginine. Recently it was shown that low plasma levels of arginine are the drive for renal arginine synthesis. In chronic renal insufficiency low plasma levels of arginine are common. To evaluate renal arginine synthesis in acute renal injury, as seen after periods of ischaemia during major vascular surgery, ischaemia–reperfusion of one kidney was performed in a rat model.
Methods: In this model of unilateral renal ischaemia–reperfusion male Wistar rats were used. Arginase infusion (ASE) was used to lower arginine plasma levels to 50 per cent of normal and control rats received saline infusion (SAL). After an

ischaemic period of 90 min, the kidney was perfused for 150 min (IR kidney). The contralateral kidney was left *in situ* and served as a control (CL kidney). Blood flow measurement was performed at the end of the experiment using radiolabelled microspheres. Blood samples were taken for amino acid analysis (high-pressure liquid chromatography). Uptake or release of arginine (flux) was calculated from flow and the arteriovenous concentration difference.

Results: Infusion of arginase efficiently decreased arginine plasma levels (ASE: mean(s.d.) 45·3(4·8) μmol/dm^3 *versus* SAL: 107·5(6·0); $P < 0{\cdot}0001$). In SAL rats, in both IR and CL kidneys a net uptake of arginine was observed (arginine flux CL kidney: + 12·5(4·9), IR kidney: + 23·6(5·8) μmol/dm^3; P not significant). Lowering arginine plasma levels by arginase resulted in production of arginine in the (non-ischaemic) CL kidney. In contrast, in the IR kidney a net uptake of arginine was seen (arginine flux CL kidney: − 5·3(2·2) μmol/dm^3, IR kidney: + 10·3(3·7) μmol/dm^3; $P < 0{\cdot}01$).

Conclusion: Synthesis of arginine by the kidney was impaired after a period of acute ischaemia–reperfusion. Ischaemia–reperfusion injury of the kidney is a condition often seen after major vascular reconstruction and impaired arginine synthesis might limit substrate for the L-arginine nitric oxide pathway.

Synergistic effects of tumour necrosis factor α and lymphotoxin α during lethal endotoxaemia

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Background: Tumour necrosis factor (TNF) α and lymphotoxin (LT) α are members of the TNF family which bind to the same receptors and which play a crucial role in the modulation of the immune response. Their differential and possible redundant roles during lethal endotoxaemia have been investigated in mice deficient in either TNF-α ($\text{TNF}^{-/-}$) or TNF-α and LT-α ($\text{TNF}^{-/-}\text{LT}^{-/-}$ double knockout) mice.

Methods: $\text{TNF}^{-/-}$ or $\text{TNF}^{-/-}\text{LT}^{-/-}$ mice were injected intravenously with *Escherichia coli* lipopolysaccharide (LPS) 1 or 2 mg per mouse. Circulating levels of interleukin (IL) 1α and 1β were measured 3 h after the LPS challenge, and mortality rates were calculated.

Results: When LPS 1 mg per mouse was used, 80 per cent of the wild-type mice succumbed, whereas none of the $\text{TNF}^{-/-}$ or $\text{TNF}^{-/-}\text{LT}^{-/-}$ mice died ($P < 0{\cdot}01$). However, when LPS 2 mg per mouse was administered, the mortality rate in the control and $\text{TNF}^{-/-}$ mice was 100 per cent, whereas none of the $\text{TNF}^{-/-}\text{LT}^{-/-}$ mice died ($P < 0{\cdot}01$), suggesting that the absence of LT-α has an additional protective effect in lethal endotoxaemia. In comparison to the wild-type control mice, 3 h after the LPS challenge, the circulating concentrations of IL-1α were 47 and 55 per cent lower in the $\text{TNF}^{-/-}$ and $\text{TNF}^{-/-}\text{LT}^{-/-}$ mice respectively. Moreover, circulating concentrations of IL-1β were 40 per cent lower in the $\text{TNF}^{-/-}$ mice, but 71 per cent lower in the $\text{TNF}^{-/-}\text{LT}^{-/-}$ mice compared with the wild-type controls.

Conclusion: TNF-α and LT-α act synergistically during lethal endotoxaemia, and immunomodulation of both TNF-α and LT-α should be considered in experimental and clinical settings.

Tumour necrosis factor α and interleukin 1β mediate lipopolysaccharide-induced endothelial monolayer permeability in whole blood

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Background: Overproduction of cytokines may be responsible for irreversible and systemic vascular damage observed among patients suffering from the sepsis syndrome. The resultant excessive fluid loss from the circulation may cause tissue hypoperfusion, organ failure and death. A whole blood assay and an *in vitro* endothelial model have been used to simulate permeability changes during the acute phase of Gram-negative infection.

Methods: Freshly drawn heparinized human blood from healthy volunteers was treated with bacterial lipopolysaccharide (LPS; *Escherichia coli* B55 : 05). Plasma was then collected and incubated on human umbilical vein endothelial cell (HUVEC) monolayers cultured on semipermeable Transwell COL membranes. The permeability of the monolayers was determined using fluorescein isothiocyanate (FITC) albumin and rhodamine-β-isothiocyanate (RITC) dextran. The production of tumour necrosis factor (TNF) α and interleukin (IL) 1β in whole blood was measured using radioimmunossay.

Results: Incubation of whole blood with as little as 10 pg ml^{-1} LPS was sufficient to yield plasma that significantly increased endothelial permeability. This effect was dose dependent up to 10 ng ml^{-1} LPS, at which the permeability exceeded about seven times the permeability of control monolayers. In contrast, significant stimulation of endothelial permeability by LPS alone (i.e. without prior incubation in blood) required more than 50 ng ml^{-1} LPS. The effect of LPS pretreatment on endothelial permeability was also time dependent: at least 2–4 h of LPS preincubation was required, while maximum permeability was reached at longer preincubations (8–24 h). At these amounts and incubation times LPS was also capable of inducing TNF-α and IL-1β in whole blood. When antibodies directed against TNF-α and IL-1β were added to LPS-conditioned plasma before incubation on HUVEC monolayers the permeability increase was partly inhibited. However, almost complete inhibition was achieved when anti-TNF-α and anti-IL-1β were both added to LPS-conditioned plasma. Similar effects of LPS-conditioned plasma and anti-TNF-α and anti-IL-1β treatment were observed on the expression of E-selectin and intracellular adhesion molecule 1 by endothelial cells.

Conclusion: Whole blood potentiates the inflammatory response of endothelial cells to physiologically relevant doses of LPS. This potentiation is achieved by the production of both TNF-α and IL-1β. If this *in vitro* endothelial model represents the events observed in patients suffering from Gram-negative sepsis, these data indicate that protection requires simultaneous administration of inhibitors to TNF-α and IL-1β.

Impairment of renal blood flow after renal ischaemia–reperfusion is not aggravated by low plasma levels of arginine

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Background: The fundamental role of the L-arginine–nitric oxide pathway has not been established for maintaining renal blood flow. Plasma levels of arginine appear to be rate limiting for nitric oxide synthesis in various cell types. Low plasma levels of arginine are seen after major surgery, trauma and sepsis. The present study was designed to establish the effects of low arginine plasma levels on renal blood flow during the initial phase of renal ischaemia–reperfusion.
Methods: In this unilateral renal ischaemia–reperfusion model, male Wistar rats were used. Arginase infusion (ASE) was used to lower arginine plasma levels to 50 per cent of normal; control rats received saline infusion (SAL). After an ischaemic period of 90 min, the kidney was perfused for 150 min (IR kidney). The contralateral kidney was left *in situ* and served as a control (CL kidney). Blood flow measurement was performed at the end of the experiment using radiolabelled microspheres. Blood samples were taken for amino acid analysis (high-pressure liquid chromatography).
Results: Infusion of arginase efficiently decreased plasma levels of arginine (ASE mean(s.d.) 45·3(4·8) μmol/dm^3 *versus* SAL 107·5(6·0) μmol/dm^3; $P < 0·0001$). In both SAL and ASE rats, a significantly lower blood flow was found in the IR kidney compared with the (non-ischaemic) CL kidney. Lowering arginine plasma levels by arginase did not influence renal blood flow compared with SAL, in both IR and CL kidneys.
Conclusion: In this acute, unilateral renal ischaemia–reperfusion model, low arginine plasma levels did not further aggravate renal blood flow.

Influence of antiseptic agents on interleukin 8 release and transmigration of polymorphonuclear granulocytes in an *in vitro* model of peritonitis

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Background: The effect of antiseptic agents on peritoneal cells is ill defined. The influence of taurolidine (TAU) and polyhexamide (HEX) was investigated in an *in vitro* model.
Methods: Human umbilical vein endothelial cells (HUVECs) and human peritoneal mesothelial cells (HPMCs) were laid on collagen-coated filter inserts (HUVECs on the bottom, HPMCs on the top), thus representing a two-chamber peritoneal model. When confluence was reached, HPMCs were stimulated with 0·5 ml tumour necrosis factor (TNF) α 10 μg ml^{-1} for 4 h. Afterwards 0·5 ml TAU (1 and 2 per cent) or 0·5 ml HEX (0·1 and 0·2 per cent) solutions were added to the upper compartment. After 1 h polymorphonuclear granulocytes (PMNs) (10^5 ml^{-1}) were added to the lower compartment. After 2 and 6 h aliquots were taken from both compartments, transmigrated PMNs were counted and interleukin (IL) 8 concentrations were measured. Controls were either TNF-α-stimulated HPMCs or stimulated HPMCs where culture medium had been substituted for TNF-α. Significance of differences was assessed by analysis of variance with Bonferroni corrections. Correlations were calculated by linear regression analysis.
Results: Stimulation with TNF-α led to a time-dependent increase in PMN transmigration. IL-8 secretion into the apical compartment increased time dependently, resulting in a gradient between the two chambers. After substitution of the stimulus by culture medium, significantly less IL-8 was measured in both compartments. PMN transmigration was almost absent. Addition of HEX resulted in an initial increase in IL-8 levels comparable to TNF controls without further changes. A concentration-dependent decrease in IL-8 gradient was associated with reduced transmigration. The IL-8 gradient between the upper and lower chambers correlated significantly with PMN transmigration ($r = 0·8205$, $P < 0·0001$).
Conclusion: The decrease in IL-8 gradients by HEX and the diminished IL-8 response after addition of TAU may reflect either anti-inflammatory effects or cellular damage. Both antiseptic solutions reduced PMN migration, irrespective of continuous stimulation in this model.

Rebound phenomenon in tissue plasminogen activator activity of parietal peritoneum after anastomosing colon in rats with bacterial peritonitis

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Background: This study aimed to measure the fibrinolytic response, which plays a role in adhesion and abscess formation, of the parietal peritoneum to surgery in the presence and absence of bacterial peritonitis.
Methods: In 48 male Wistar rats bacterial peritonitis was induced using caecal ligation and puncture (CLP). Some 24 h after CLP (day 0), 12 rats were killed and biopsies were taken from the parietal peritoneum. The remaining 36 rats were

reoperated whereby the ligated caecum was resected followed by resection of a 1-cm segment of the descending colon and end-to-end anastomosis. Thirty additional rats underwent resection of a 1-cm segment and anastomosis of the descending colon without any previous procedure. One-third of the rats were killed on days 1, 3 and 7 after anastomosing the colon, and biopsies were taken from the parietal peritoneum. From ten untreated rats, biopsies were taken for measurement of baseline levels. All biopsies were homogenized and tissue plasminogen activator (tPA) activity was measured using an enzyme-linked immunosorbent assay.

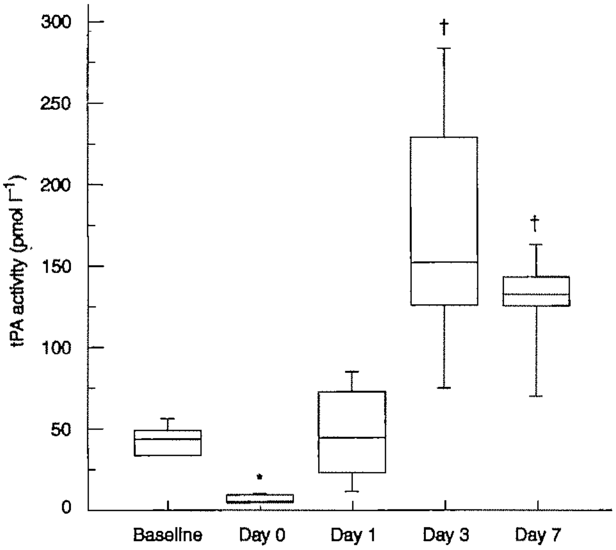

Fig. 1 tPA activity in biopsies from the parietal peritoneum. $^*P < 0{\cdot}0001$, $^\dagger P = 0{\cdot}0002$ *versus* baseline

Results: Some 24 h after inducing peritonitis (day 0), tPA activity was significantly ($P < 0{\cdot}0001$) decreased compared with baseline levels. One day after anastomosis in rats with peritonitis, tPA activity was in the same range as baseline values, while tPA activity was significantly increased on days 3 and 7 after anastomosis, in comparison to baseline levels ($P = 0{\cdot}0002$). There was no significant difference in tPA activity compared with baseline levels 1, 3 and 7 days after anastomosing colon in normal rats.

Conclusion: In rats with bacterial peritonitis, tPA activity in the parietal peritoneum was depressed after 24 h; 24–48 h after inducing peritonitis, tPA activity increased, reaching supranormal levels at days 3–7. Surgery alone does not influence tPA activity of the parietal peritoneum.

Administration of nitric oxide restores the abolished hepatic artery buffer responses in early porcine endotoxaemia

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Background: Among other organs, the liver may be severely compromised by the altered haemodynamic conditions of septic shock. The hepatic artery buffer response (HABR), which is mediated mainly by adenosine 5′-triphosphate and nitric oxide as the second messenger, and is ablated during endotoxaemia, plays a central role in the autoregulation of liver perfusion. It was hypothesized that a temporarily decreased synthesis of nitric oxide during early endotoxaemia might be responsible for the dysfunction of the HABR and that administration of nitric oxide could re-establish the autoregulation of hepatic blood flow.

Methods: The experiment was performed in 15 juvenile Landrace pigs, which were randomly assigned to receive endotoxin (ET) 1·7 μg kg^{-1} min^{-1} (*Escherichia coli*) and the non-enzymatic nitric oxide donor sodium nitroprusside (SNP) 3 μg kg^{-1} min^{-1} (ET-SNP group; $n = 7$) or ET 1·7 μg kg^{-1} min^{-1} (*E. coli*) and vehicle (ET group; $n = 8$). ET and nitric oxide were administered into the portal vein. Study measurements (haemodynamic measurements, liver perfusion) were performed for 5 h.

Results: ET caused a significant decrease in liver perfusion after 5 h. Hepatic arterial flow (Q_{ha}) was reduced by 50 per cent and portal vein flow (Q_{pv}) by 38 per cent. The additional administration of nitric oxide ameliorated liver perfusion; Q_{ha} and Q_{pv} were not altered significantly in the ET-SNP group. The mechanical reduction of Q_{pv} to approximately 50 per cent of baseline increased Q_{ha} in all animals before administration of ET. Flow increase in the hepatic artery due to partial Q_{pv} occlusion (HABR) was lost in the ET group, while nitric oxide preserved a mean increase of 28 per cent in Q_{ha} ($P < 0{\cdot}01$). At time zero the Q_{pv} reduction decreased mean hepatic artery resistance (HAR) in both groups. Thereafter ET infusion led to a continuous loss of the response of HAR to reduction of Q_{pv}, while nitric oxide administration kept the response of HAR at pre-ET levels throughout the experiment. At 4 and 5 h the reactivity of HAR to manipulations of Q_{pv} had returned to baseline levels in the ET group.

Conclusion: Early administration of the non-enzymatic nitric oxide donor SNP during endotoxaemia is able to re-establish an autoregulatory response of the hepatic artery following reduction of hepatic blood flow.

Investigation of a potential effect of exogenous interleukin 10 on lipopolysaccharide mediated tolerance to lipopolysaccharide in rabbits

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Background: Postoperative immunosuppression is a risk factor for postoperative infection and sepsis. The lipopolysaccharide (LPS) sensitivity of circulating leucocytes is diminished in the postoperative course. A similar state of LPS tolerance can be induced in the experimental setting by injection of low doses of LPS. This tolerance may be mediated by cytokines which are released following LPS injection. In the presence of interleukin (IL) 10 the LPS-induced production of numerous cytokines is diminished in leucocytes. The aim of the study was to investigate the effect of exogenous IL-10 on LPS-induced tolerance to LPS in rabbits.

Methods: Rabbits were injected intravenously with LPS 5 $\mu g\,kg^{-1}$ or human recombinant IL-10 (hrIL-10) 5 $\mu g\,kg^{-1}$ or with sodium chloride or hrIL-10 1 h before LPS. Blood was drawn thereafter repeatedly up to the fifth day and incubated without or with LPS (10 $ng\,ml^{-1}$, 1000 $ng\,ml^{-1}$) for 20 h. Tumour necrosis factor (TNF) α was assayed in plasma supernatants using the L929 bioassay and hrIL-10 was detected in serum samples by enzyme-linked immunosorbent assay. Rectal temperature was measured at the indicated time points.

Results: Injection of LPS transiently (3 days) caused a biphasic fever and a LPS-tolerant state. IL-10, like LPS, transiently diminished the capacity for TNF-α production. The administration of IL-10 1 h before the injection of LPS neither affected the LPS-induced suppression of TNF-α production, nor modified the duration of tolerance. Likewise, fever curves were no different.

Conclusion: This pilot study shows that, despite IL-10-induced reduction of the capacity for (proinflammatory) cytokine production, LPS tolerance following LPS injection was not altered. Thus systemic cytokine production seems not to be responsible for the induction of fever and LPS tolerance.

Timing of endothelin and nitric oxide inhibition is crucial for survival in septic shock

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Background: The effect of endothelin and nitric oxide inhibition on survival from septic shock was investigated in mice, with particular emphasis on the timing of the administration of their blockers after an endotoxin (lipopolysaccharide; LPS) challenge.

Methods: Male Swiss albino mice (20–40 g) received LPS (*Escherichia coli* 055 : B5; 60 $mg\,kg^{-1}$ intraperitoneally) followed by intraperitoneal injection of the endothelin receptor antagonist bosentan 30 $mg\,kg^{-1}$, either 2 or 12 h after LPS, alone or in addition to intraperitoneal nitric oxide synthase blockers L-canavanine 20 or 100 $mg\,kg^{-1}$, L-NAME 3 $mg\,kg^{-1}$ or aminoguanidine 15 $mg\,kg^{-1}$, which were given twice, at 2 and 6 h after LPS. Control animals received saline and survival rates in each group ($n = 10$) were recorded over 24 h at 6-h intervals.

Results: At 24 h, the survival rate was 10 per cent in controls, but 30 per cent (P not significant) and 70 per cent ($P < 0{\cdot}05$) in animals that received bosentan only at 2 and 12 h respectively, indicating a relatively 'late' involvement of endothelin. In contrast, these values were 70 per cent ($P < 0{\cdot}05$) and 80 per cent ($P < 0{\cdot}05$) at 12 h for L-NAME and L-canavanine, which both decreased to 10 per cent (P not significant) at 24 h implying a relatively 'early' involvement of nitric oxide. A higher value (60 per cent; $P < 0{\cdot}05$) was obtained when bosentan given at 2 h was combined with L-NAME. The best outcome (90 per cent survival rate; $P < 0{\cdot}05$) was observed when bosentan was given at 12 h in combination with L-NAME at 2 and 6 h. Interestingly, the survival rate was 70 per cent ($P < 0{\cdot}05$) in the aminoguanidine group, which can be explained by other pharmacological effects of this drug in addition to nitric oxide blockade.

Conclusion: Nitric oxide plays a significantly deleterious role during the early phases of septic shock, in contrast to a relatively late involvement of endothelin peptides. This should be taken into consideration when devising treatment strategies.

Gram-positive bacterial cell wall products upregulate surface expression of intercellular adhesion molecule 1, human leucocyte antigen DR and CD14 on monocytes in human whole blood

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Background: The aim was to investigate the influence of Gram-positive cell wall components on monocyte surface inflammatory receptors compared with lipopolysaccharide (LPS) in human whole blood.

Methods: Human whole blood from six healthy donors was incubated with peptidoglycan (PepG) 10 $\mu g\,ml^{-1}$ from *Staphylococcus aureus* and *Bacillus subtilis*, lipoteichoic acid (LTA) 100 $\mu g\,ml^{-1}$ from *S. aureus* and LPS 10 $ng\,ml^{-1}$ from *Escherichia coli* in microcentrifuge tubes at 37°C with slow rotation for 4 h. Subsequent to incubation with fluorescein isothiocyanate (FITC)- and phycoerythrine (PE)-labelled monoclonal antibodies, surface molecule (CD14, CD54, CD58, CD64, CD80 and human leucocyte antigen (HLA) DR) expression was analysed by flow cytometry performed on the FACScan using the CellQuest software.

Results: All surface molecules except CD80 were expressed constitutively on monocytes in whole blood. Stimulation with either type of PepG, LTA and LPS did not induce any changes in expression of CD58 or CD64, nor did they induce expression of CD80. However, significant upregulation of CD54 and HLA-DR was observed in all donors. Contrary to LPS, PepG and LTA also upregulated the expression of monocyte surface CD14.

Conclusion: The Gram-positive cell wall products PepG and LTA strongly upregulated the expression of intercellular adhesion molecule 1 (CD54) and HLA-DR on monocytes in human whole blood, as was seen in LPS-stimulated whole blood. In contrast to Gram-negative endotoxin, the Gram-positive cell wall products also upregulated the expression of the LPS receptor CD14. This suggests possible differences in intracellular signalling between Gram-positive cell wall products and Gram-negative LPS in monocytes.

Kinetics of tumour necrosis factor α and interleukin 10 in rats with endotoxaemia and obstructive jaundice-induced anergy

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Background: Obstructive jaundice leads to a significant increase in septic complications. In addition, endotoxaemia may cause a secondary insult. The effects of endotoxaemia and obstructive jaundice-induced anergy on the kinetics of two early mediators of the response to sepsis, tumour necrosis factor (TNF) α and interleukin (IL) 10, were investigated.

Methods: Wistar rats had either bile duct ligation (BDL) or sham operation. After 2 weeks, anergy was confirmed by a delayed-type hypersensitivity response in rats that had undergone BDL. All rats were challenged with *Escherichia coli* lipopolysaccharide (LPS) 20 mg kg^{-1} or saline. After 90 and 180 min, rats were killed and blood samples were obtained for TNF-α and IL-10 measurement.

Results: There was no intragroup difference after saline challenge. LPS injection significantly increased both TNF-α and IL-10 levels in all groups compared with all saline injection groups. LPS injection following BDL led to significantly higher TNF-α levels and lower IL-10 levels at 90 min compared with those after sham operation ($P < 0\cdot05$). There were no differences between TNF-α and IL-10 levels at 180 min following LPS challenge in rats that had undergone BDL.

Conclusion: BDL primes for an increase in TNF-α levels to a subsequent LPS challenge. However, the IL-10 increase following an LPS challenge is suppressed by BDL. These results suggest that BDL primes for a more vigorous inflammatory response to LPS challenge.

Immune dysfunction following haemorrhage can be restored by interleukin 10 in males but not in females

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Background: Recent studies have shown depressed immune responses following haemorrhagic shock in males, whereas they are enhanced in females. Furthermore, this results in a lower mortality rate in females following subsequent sepsis. Interleukin (IL) 10 has been shown to play a potential role in treatment of the early proinflammatory state following haemorrhagic shock. Although beneficial effects of treatment with IL-10 have been shown, it remains unclear whether the effects are sex related.

Methods: Male and female CBA/J mice were subjected to haemorrhage (35 ± 5 mmHg for 90 min and fluid resuscitation) or sham operation. At resuscitation each received either intraperitoneal recombinant murine IL-10 or placebo. *In vitro* splenic T cell responses were determined 48 h after resuscitation.

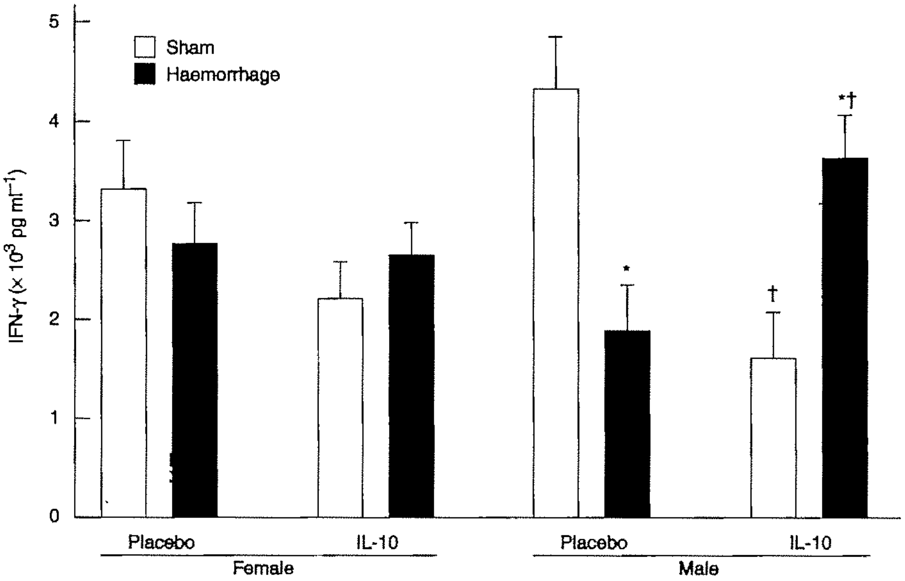

Fig. 1 Mean(s.d.) interferon (IFN) γ levels after haemorrhagic shock or sham operation in male and female rats. *$P < 0\cdot05$ *versus* sham; †$P < 0\cdot05$ *versus* placebo

Results: IL-10 release of splenocytes was not enhanced after IL-10 treatment. Proinflammatory immune function was depressed (i.e. proliferation, IL-2, IFN-γ) in males receiving placebo compared with no change in females. IL-10 treatment restored the depressed proinflammatory immune response in males following haemorrhagic shock (*Fig. 1*). In contrast, the immune response in females receiving IL-10 was not significantly changed. However, IL-10 treatment of sham-operated male mice led to immune depression compared with placebo-treated animals.

Conclusion: Early IL-10 anti-inflammatory treatment following haemorrhage has potential beneficial effects in males only.

Fungal prophylaxis in biliopancreatic surgery in immunocompromised patients

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Background: Fungal infection is a devastating complication with an increased incidence in the past decade. Immune-depressed patients undergoing high-risk procedures have an increased incidence of surgical infection, particularly due to fungal colonization.

Methods: Twenty patients undergoing pancreas transplantation, 20 kidney transplant patients undergoing biliary tract surgery, 20 patients with human immunodeficiency virus (HIV) undergoing biliary tract surgery and 20 patients undergoing pancreatic resection for neoplasms were enrolled in a prospective study concerning perioperative surgical infection. All patients underwent surgical procedures by the same surgeon. All had preoperative blood counts, assay of CD lymphocyte populations, complete nutritional evaluation and similar antibiotic prophylaxis. Perioperative care was done to a similar standard and only patients undergoing pancreas transplantation received fungal prophylaxis (nystatin wash and swallow). In patients with clinical signs of infection, cultures were sent with special consideration to fungal infection.

Results: Two of the patients undergoing pancreas transplantation (one of whom died from disseminated candidiasis), three of the kidney transplant patients (two on the wound, one in the catheter), three patients with HIV (two on bile culture, one in the bloodstream) and one of the patients undergoing pancreatic resection (pancreatic fistula and bloodstream) had fungal infection. All patients had concomitant bacterial infections at the time of fungal infection (60 per cent *Staphylococcus epidermidis*). Patients with fungal infection had increased levels of immunosuppression with decreased CD4 recounts (pancreas transplants and patients with HIV), increased perioperative levels of blood glucose requiring insulin treatment, prolonged antibiotic therapy with broad-spectrum antibiotics (piperacillin–tazobactam), previous positive cultures from the bile of the biliary tract or the duodenum of the transplanted pancreas, and concomitant bacterial infections (especially opportunistic).

Conclusion: Surgical patients with positive cultures from surgical specimens, prolonged broad-spectrum antibiotic therapy and severely decreased lymphocyte immune function had an increased incidence of fungal infection with significant morbidity and mortality rates. Fungal prophylaxis is strongly recommended in these high-risk patients undergoing biliopancreatic tract surgery.

Hyperglycaemia is associated with fungaemia and an increased mortality rate in severely burned children

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Background: Hyperglycaemia may have detrimental effects on immunity. The purpose of this study was to assess any relationship between hyperglycaemia and clinical outcome following injury.

Methods: The records of children with burns covering 60 per cent or more of the body surface admitted after 1996 were reviewed. Patients were categorized as having poor glucose control if 40 per cent or more of all plasma glucose determinations were 7·8 mmol l^{-1} or greater and were compared with patients with adequate glucose control (less than 40 per cent of glucose values 7·8 mmol l^{-1} or greater).

Results: Despite similar age, burn size and caloric intake, the extent and severity of hyperglycaemia was significantly greater in the 33 patients categorized as having poor glucose control than in the 25 patients with adequate glucose control. Patients with hyperglycaemia had a significantly higher proportion of blood cultures positive for yeast (mean(s.d.) 3·7(10·0) *versus* 0·1(0·7) per cent; $P < 0{\cdot}05$, Student's *t* test). Nine of 33 patients with persistent hyperglycaemia died, compared with only one of 25 with adequate glucose control ($P \leqslant 0{\cdot}05$, Fisher's exact test).

Conclusion: This association between hyperglycaemia, fungaemia and subsequent death in severely burned children may be related to a hyperglycaemia-induced deterioration in immune function. This suggests that aggressive manoeuvres to normalize plasma glucose may be warranted.

Risk factors in surgical patients with intra-abdominal *Candida* infection in intensive care

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Background: *Candida* species have been isolated with increasing frequency during intra-abdominal infection, yet their role as pathogens or co-pathogens and as determinants for outcome, especially in patients who are frequently reoperated on, is not well understood. Furthermore, the value of antimycotic therapy is the subject of discussion.

Methods: *Candida* cultures from the abdomen of surgical patients over the past 10 years (1989–1999) were documented. Medical records of the patients were reviewed for risk factors for morbidity and death.

Results: Some 72 patients (45 men, 27 women), of mean age 60 (range 18–88) years, had *Candida* cultured from the abdomen during operation. Indications for surgery included duodenal ulcer perforation in 15 patients (21 per cent), gastrointestinal malignancy in 15 (21 per cent), pancreatitis in nine (12 per cent) and various disorders in the remaining 33. A total of 361 relaparotomies was performed in 72 patients (mean 5, range 0–48). Cultures were positive at the first laparotomy in 19 patients, at the first relaparotomy in 20 patients and in 33 patients at the second or more relaparotomy. All but one patient were treated in the intensive care unit. Some 45 (62 per cent) of 72 patients died a mean of 44 (range 3–234) days after the first laparotomy. Risk factors for death, which appeared not to be significant, are shown in the Table.

	Died (*n*=45)	Survived (*n*=27)
No. of relaparotomies*‡	5·3 (0–48)	4·5 (0–35)
No. of co-morbid factors*	1·7 (0–4)	1·4 (0–4)
Positive blood culture for *Candida*†	7 (16)	3 (11)
Patients treated with AMT†	35 (78)	14 (52)
Time to start of AMT (days)*§	3·8 (0–18)	7·9 (0–21)
Grade of infection*	2·2 (0·5–4)	1·7 (0·5–4)
No. of bacterial types in abdominal cultures*	3·4 (0–8)	3·4 (0–8)
Renal failure†	16 (36)	7 (26)

*Values are mean (range); †values in parentheses are percentages. ‡Daily 'open' abdomen wound lavage is counted as relaparotomy. §From identification of positive culture. AMT, antimycotic treatment

Conclusion: The number of relaparotomies among patients with *Candida*-positive cultures was high. No significant risk factors for death could be identified in surgical patients with intra-abdominal *Candida* infection in intensive care.

Requirement for fungal prophylaxis in high-risk surgical patients: a randomized trial

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Background: In previous studies the authors have selected patients and surgical procedures with a high risk of fungal infection. Whether these patients and procedures require fungal prophylaxis was studied.

Methods: From June to December 1999, 850 surgical patients from two university hospitals were enrolled in a prospective open randomized study. Fifty were selected according to demographics (age, sex, co-morbidity) and surgical procedures (defined by GDRs and ICD9-CM) as at high risk of fungal infection according to a previously defined algorithm (presented to the Surgical Infection Society of Europe 1999). In these 50 patients the CD lymphocyte population was recollected, and urine, blood, sputum and wound (if infected) cultures were performed. Then, 25 were treated with nystatin wash and swallow, and the others with placebo. Fungal infection and fungal colonization were defined and used as the endpoint of the study.

Results: Patients not selected for the study did not develop fungal infection. Of the high-risk patients, 20 presented with fungal colonization (12 urine, seven wound and five bloodstream cultures) and 12 presented with subsequent fungal infections. Of these 20 colonized patients, only those with nystatin prophylaxis did not require fungal treatment, whereas controls required treatment. CD4 lymphocyte recount (below 300) was uniformly decreased in all patients with fungal infection.

Conclusion: Immunodepressed patients at high risk with concomitant fungal colonization develop fungal infections 2–5 days after high-risk surgical procedures. Nystatin prophylaxis in such patients may reduce the degree and severity of fungal infection. If fungal colonization is present and the CD4 lymphocyte count is below 300, fungal treatment might be advisable.

pH-dependent activity of amphotericin B

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Background: Abscesses caused by *Aspergillus* spp. are a rare presentation of invasive disease but commonly occur in patients with chronic granulomatous disease (CGD). Although amphotericin B (AmB) is considered standard treatment for these patients, up to 85 per cent of patients fail to respond. Several patients have been reported to respond after treatment was changed to antifungal azoles including itraconazole (ITZ) and voriconazole (VCZ). Although the underlying defect in the host defence is the most important cause of failure, the activity of AmB might be reduced in the local environment inside the abscess. Since pH has been shown to be low in abscesses, the effect of pH on the *in vitro* activity of AmB and ITZ was investigated.

Methods: Two *A. fumigatus* isolates and one *A. nidulans* isolate were cultured from patients with CGD. Two of these patients had failed to respond to treatment with AmB and had responded to treatment with VCZ. Serial twofold dilutions of AmB and ITZ were made in RPMI-1640 and buffered with MOPS at a pH of 4·0, 5·0, 6·0 and 7·0. The minimum inhibitory concentration (MIC) for each isolate was determined after 24 and 48 h of incubation by visual reading.

Results: For all isolates, the MIC of AmB and ITZ at pH 7·0 was 0·25 and 0·06 mg l^{-1} respectively. The MIC of AmB increased significantly with decreasing pH resulting in a MIC of 16 mg l^{-1} at pH 4·0. However, the MIC of ITZ was not affected by the pH of the medium. Although breakpoints have not been established for AmB, MIC values above 0·5 mg l^{-1} correspond to clinical failure in patients with yeast infection.

Conclusion: The reduced activity of AmB at low pH might contribute to the failure of patients with fungal abscesses to respond to treatment with AmB. Primary therapy with azoles may be warranted.

Treatment of *Candida* infection in patients with infected pancreatic necrosis

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Background: The purpose of this review was to determine the incidence of *Candida* infection in patients with infected pancreatic necrosis, to determine the most frequent risk factors and to assess the best treatment approach for disseminated candidal infections.

Methods: Of 145 patients with infected pancreatic necrosis identified, 30 (21 per cent) were infected with *C. albicans*. Risk factors identified in patients with *Candida* infection included the presence of necrotic tissue, and the use of broad-spectrum antibiotics, intravascular catheters and parenteral nutrition.

Results: With one exception, all cases involved mixed bacterial and fungal infections. The positive fungal result was obtained either during or after operation. Sixteen of the 30 patients displayed fungal colonization, while the other 14 had disseminated fungal infection. There were two deaths in the disseminated group, but none in the colonization group. In both fatal cases, flucytosine was applied. When fluconazole was used against disseminated fungal infection, no death was noted. Recently, prophylactic fluconazole has also been used in 20 patients with infected pancreatic necrosis, with no evidence of fungal infection after operation.

Conclusion: The combination of adequate surgical treatment with effective antibiotics and early antifungal therapy is the ideal management approach for infected pancreatic necrosis with *Candida* infection. Fluconazole may be regarded as an efficient drug for the prophylaxis of candidiasis.

Role of cytokines of the tumour necrosis factor family in the immune response to disseminated *Candida albicans* infection

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Background: Tumour necrosis factor (TNF) α, lymphotoxin (LT) α, CD40L and FasL are members of the TNF family that play a crucial role in modulation of the immune response. Their role in the defence against infection with *Candida albicans* was investigated in mice deficient in either TNF-α and LT-α ($TNF^{-/-}LT^{-/-}$ mice), CD40L ($CD40L^{-/-}$ mice) or Fas (MRL/lpr mice).

Methods: Mortality rates were compared in mice infected intravenously with 10^6 colony-forming units of *C. albicans* per mouse.

Results: After infection with *C. albicans* the $TNF^{-/-}LT^{-/-}$ mice had a significantly increased mortality rate compared with control mice (100 *versus* 40 per cent; $P < 0·01$). This was due to a 10–1000-fold increased outgrowth of the yeasts in the kidneys and liver of $TNF^{-/-}LT^{-/-}$ mice ($P < 0·01$). Defective recruitment and phagocytosis, but not *Candida* killing, were responsible for these effects. $CD40L^{-/-}$ mice were also more susceptible to systemic candidiasis than the wild-type controls (mortality rate 80 *versus* 50 per cent; $P < 0·05$), and the growth of *Candida* in the kidneys was one order of magnitude higher in the deficient than in control mice ($P < 0·05$). Neutrophil function in the $CD40L^{-/-}$ mice was normal, whereas decreased *Candida* killing by macrophages through nitric oxide-dependent mechanisms was responsible for the effect of CD40/CD40L interactions. In contrast, Fas-defective MRL/lpr mice were significantly more resistant to disseminated candidiasis (mortality rate 50 *versus* 100 per cent; $P < 0·01$); this was mediated by the facilitation of neutrophil migration to the site of infection.

Conclusion: Cytokines of the TNF family play a crucial role in the modulation of host defence against fatal *C. albicans* infection. Their effects are exerted selectively at the level of neutrophil or macrophage function.

Role of tumour necrosis factor α in intra-abdominal abscesses caused by *Candida albicans*

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Background: The incidence of various *Candida* spp. as a cause of nosocomial infections has increased. Patients undergoing abdominal surgery are at risk of intra-abdominal and invasive candidiasis. The mortality rate among patients with abdominal *Candida* sepsis is high. The proinflammatory cytokine tumour necrosis factor (TNF) α plays a pivotal role in the pathogenesis of sepsis and septic shock. Animal experiments have shown that neutralization of endogenous TNF-α using monoclonal antibodies has a beneficial effect on the mortality rate associated with bacteraemia. However, clinical trials using anti-TNF-α monoclonal antibodies or soluble TNF-α receptors in patients with sepsis are disappointing. The requirement of TNF-α for mounting a host defence and its beneficial effect on granuloma formation may explain these results. During

disseminated candidiasis in mice, the mortality rate is increased in absence of endogenous TNF-α and lymphotoxin (LT) α. TNF-α and LT-α promote the recruitment of granulocytes at the site of infection and phagocytosis of *Candida* blastospores.
Methods: To investigate the role of TNF-α in a model of localized *Candida* infection (i.e. abdominal sepsis and abscess formation), a mixture of sterile faeces and *Candida albicans* was injected into the peritoneal cavity of TNF/LT double knock-out (TNF$^{-/-}$ LT$^{-/-}$) mice and their wild-type (TNF$^{+/+}$ LT$^{+/+}$) counterparts.
Results: Similar to TNF$^{+/+}$ LT$^{+/+}$ mice, TNF$^{-/-}$ LT$^{-/-}$ mice developed intra-abdominal abscesses. However, while TNF$^{+/+}$ LT$^{+/+}$ mice tended to recover from infection, the number of abscesses and fungal load of the abscesses continued to increase in TNF$^{-/-}$ LT$^{-/-}$ mice.
Conclusion: TNF-α and LT-α are not critical to the process of abscess formation, except for the elimination of *Candida* from abscesses. These results suggest that anti-TNF-α therapy is not desirable in abdominal *Candida* sepsis.

Immunomodulation with granulocyte–macrophage colony-stimulating factor and interleukin 2 in an experimental model of sepsis

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Background: Previous studies have demonstrated that immunomodulation with granulocyte–macrophage colony-stimulating factor (GM-CSF) reduces the mortality rate in an experimental model of sepsis, decreases levels of tumour necrosis factor in the serum and in the liver, and enhances neutrophil activity. It was also demonstrated recently that immunoprophylaxis with interleukin (IL) 2 can reduce the mortality rate in rats that have undergone caecal ligature and puncture (CLP). In fact, IL-2 is the major activator of the specific immune response (B and T lymphocytes). The aim of this study was to investigate whether IL-2 and GM-CSF together might further decrease the mortality rate in an experimental model of peritonitis in rats, which resembles the clinical situation of bowel perforation and mixed bacterial peritonitis.
Methods: Peritonitis was induced by CLP in four groups of Sprague–Dawley male rats (250 g). Each group included 30 rats. Group 1 underwent CLP and postoperative antibiotic therapy with tobramycin and clindamycin (12·5 μg g^{-1} day^{-1} and 4 mg g^{-1} day^{-1} respectively for 72 h after operation). Group 2 underwent preoperative intraperitoneal IL-2 injection (1.000.000 units), then CLP and postoperative antibiotic therapy with the same regimen. Group 3 underwent CLP and intraperitoneal GM-CSF injection (1 ng g^{-1} day^{-1} for 48 h after operation). Group 4 received IL-2, CLP and GM-CSF with the same regimen and antibiotic therapy. Deaths were recorded within 72 h after CLP.
Results: After CLP group 1 (antibiotics) had a mortality rate of 70 per cent; group 4 (IL-2, GM-CSF, antibiotics) had a mortality rate of only 3 per cent which was significantly lower than in that in group 2 (IL-2 and antibiotics) and group 3 (GM-CSF and antibiotics), 33 and 25 per cent respectively (P < 0·0001).
Conclusion: Only one of 30 rats that had CLP and were treated with IL-2, GM-CSF and antibiotics died. Immunomodulation offers a new option in the treatment of sepsis related to peritonitis; in this experimental model treatment with IL-2 and GM-CSF enhanced host resistance to sepsis and decreased the mortality rate.

Short- and long-term effects of perioperative homologous blood transfusion in surgical patients with cancer

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Background: The immunosuppressive effect of transfusion with homologous blood is debated. The aim of this study was to find the potential correlation between the use of homologous blood in the perioperative period and postoperative infection (short-term effect) and survival (long-term effect) in patients undergoing gastrointestinal surgery for cancer.
Methods: A total of 1010 patients with a gastrointestinal neoplasm (316 gastric, 694 colorectal) having major surgical procedures were observed prospectively. The following variables were recorded: sex, age, type and duration of operation, operative blood loss, type and amount of blood transfusion, type and rate of postoperative complications, disease stage (tumour node metastasis (TNM) or Dukes), and use of adjuvant therapy (radiochemotherapy). The χ^2 test was applied to correlate discrete variables. Cox multiple regression analysis was used to evaluate the impact of each single variable on survival. Five-year survival curves were studied by the Kaplan–Meier method and their correlation was made by the log rank test.
Results: According to the Cox model, in patients who underwent gastrectomy there was a significant correlation (P < 0·01) only between age, disease stage and 5-year survival rate. The odds ratio for the relationship between homologous transfusion and survival was 1·43 (P = 0·08). When overall 5-year survival was split by TNM class, homologous transfusion significantly affected the mortality rate for patients in stage II and III (P < 0·05), while survival in patients of stage I and IV was not influenced by the use of homologous blood. Similar results were obtained in subjects with colorectal cancer, with the difference that in the Cox multivariate analysis homologous transfusion was significantly correlated with the overall 5-year survival rate (P < 0·005). Again, the strongest correlation was observed for intermediate disease stages (Dukes B and C). The χ^2 value for the linear trend also showed a significant relationship between the amount of blood transfused and 5-

year survival rate. In this population there was also a statistically significant correlation between transfusion and the rate of postoperative infections ($P = 0.001$).
Conclusion: The correlation between homologous blood transfusion and short- and long-term immunosuppression appears to be valid dependent on the site of the neoplasm, particularly for patients with an intermediate disease stage.

Implementing a randomized controlled trial with granulocyte colony-stimulating factor prophylaxis to improve the outcome of high-risk patients with colorectal cancer in the complex clinical setting of multiple surgical interventions

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Background: All large multicentre trials with immune modifiers in sepsis faded despite promising preclinical results. Several reasons for this have been discussed in the literature and include patient heterogeneity, different phases of pathophysiological state and trial errors. There are two additional and important points: the interaction of immune modifiers with the complex clinical management was not analysed preclinically and in multicentre trials the surgical management was not standardized.
Methods: Before implementing the clinical trial, the interaction of granulocyte colony-stimulating factor (G-CSF) with various surgical interventions was analysed in clinical modelling randomized trials (CMRTs) in rats, including different antibiotics, heparin, H_1 and H_2 antagonists, abdominal lavage, and management of preoperative and intraoperative bleeding. Good clinical practice rules were applied and the complexity of clinical reality was modelled in the CMRTs. In the clinical trial, high-risk patients (American Society of Anesthesiologists grades III and IV) with colorectal cancer were identified and randomized to the placebo and G-CSF groups ($n = 40$ per group). G-CSF prophylaxis (300 μg) was given subcutaneously 12 h before, and 12 and 36 h after operation. The three primary endpoints were health status measured with a modified McPeek index over 6 months, self-reported quality of life determined with the European Organization for the Research and Treatment of Cancer QLQ38 questionnaire and the true endpoint defined 6 months after operation.
Results: Implementation of the trial demonstrated that a high standardization of surgical management is not possible in multicentre trials since the surgical management of patients with colorectal cancer is heterogeneous and management of the most important complication, anastomotic leakage after colorectal surgery, is performed according to personal experience and is not based on high levels of evidence from clinical trials low evidence based medicine (EBM). For this reason the surgical management of patients in the trial should be defined, a centre-based clinical guideline for the management of anastomotic leakage applied and adherence to the guideline recorded.
Conclusion: Without CMRTs to analyse the interaction of immune modifiers in complex settings and defined clinical management of patients, no positive results will be obtained from such clinical trials.

Translocation of *Enterococcus* in jaundiced and anergic rats

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Background: Translocation of bacteria from the gut to other organs is one cause of systemic complications in obstructive jaundice. Furthermore, hyperbilirubinaemia appears to cause anergy. This study investigated whether these responses (translocation of gut bacteria and anergy) increase the postoperative mortality rate in rats in which obstructive jaundice is induced surgically by ligature of the bile duct.
Methods: Some 88 male Wistar rats were divided into six groups. All rats except those in group 1 received gentamicin by the oral route (0·7 mg in 1 ml water, daily for 6 days) to ensure intestinal decontamination. On day 7, all rats except those in groups 1 and 2, which had vehicle only, received *Enterococcus*. Statistical analysis was by Student's test and Fishers's exact test.

Group	Gentamicin	*Enterococcus*	Operation
1	–	–	–
2	+	–	–
3	+	+	–
4	+	+	Sham
5	+	+	CBD ligation
6	+	+	CBD ligation and section

CBD, common bile duct

All animals underwent standard blood testing, delayed hypersensitivity tests, haematimetry and serum endotoxin determinations. Flow cytometry was used to count CD3-, CD4- and CD8-positive lymphocytes. On the day 5 after surgery, these assays were repeated and, in addition, the rats were killed for microbiological analysis of gut and viscera contents (liver, spleen, mesentery and lung).
Results: Five days after surgery, mean bilirubin levels in groups 5 and 6 were greater than $14\,\mathrm{mg\,dl^{-1}}$. In addition, all rats in groups 5 and 6 showed absence of the delayed hypersensitivity response, indicating anergy. Lymphocyte counts in each group are shown in the *Table*.

	Lymphocyte counts (%)					
	1	2	3	4	5	6
CD3	76	76	67	65	51	51
CD4	46	49	47	47	30	34
CD8	24	26	16	17	15	15

The mean proportion of CD8-positive lymphocytes in rats that had received *Enterococcus* (groups 3–6) was 16 per cent compared with 25 per cent in groups 1 and 2 ($P < 0{\cdot}05$). The mean percentage of CD3-positive lymphocytes in groups 5 and 6 was 51 per cent, but 71 per cent in all other groups ($P < 0{\cdot}05$). Likewise, the mean percentage of CD4-positive lymphocytes in groups 5 and 6 was 32 per cent, but 47 per cent in all other groups ($P < 0{\cdot}05$). The postoperative mortality rate in group 4 (17 per cent) was significantly lower than that in the obstructive jaundice groups 5 and 6 (62 per cent) ($P < 0{\cdot}01$). Post-mortem microbiological analyses revealed translocation of *Enterococcus* only in groups 5 (80 per cent) and 6 (70 per cent). Enterococci were most frequently present in the mesentery (80 and 70 per cent respectively), followed by the liver (40 and 40 per cent), spleen (20 and 20 per cent) and lungs (10 and 10 per cent).
Conclusion: (1) Obstructive jaundice in rats leads to immunological alterations including anergy. (2) Obstructive jaundice in rats favours translocation of enterococci from the gut to other organs. (3) The postoperative mortality rate in jaundiced rats was much higher than that in sham-operated rats.

Bacterial overgrowth and translocation in an experimental pancreatitis model

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Background: A combination of secretory hyperstimulation and transduodenal intraductal bile acid exposure results in homogeneous pancreatitis with graded severity in a rat model. The model was modified by using an exteriorized common bile duct (CBD) as ductal infusion port while keeping the integrity of the gut intact. The objective was to determine whether bacterial translocation (BT) is present and relates to small bowel bacterial overgrowth (SBBO).
Methods: Fifty rats were divided into four groups: group 1, mild pancreatitis (intravenous caerulein); group 2, control (intravenous saline); group 3, necrotic pancreatitis (intravenous caerulein, intraductal glycodeoxycholic acid); and group 4, control (intravenous and intraductal saline). During infusion the CBD was clamped just above the papilla of Vater. Three days later samples from peripheral blood, peritoneal fluid and abdominal organs were harvested for quantitative microbial culturing. The splenic portion of the pancreas was removed for histopathological analysis.
Results: Histological examination showed minimal oedema in groups 2 and 4; group 1 was characterized by acinar vacuolization and group 3 had a combination of acinar necrosis with inflammation. BT to one or more abdominal organs took place. The difference in incidence of translocation between group 1 (six of 14) and group 2 (none of eight) was significant ($P < 0{\cdot}05$). Furthermore, there was a significant difference in translocation between group 3 (six of eight) and group 4 (one of six) ($P < 0{\cdot}05$), and in duodenal total bacterial counts between groups 3 and 4 ($P < 0{\cdot}05$). Gram-negative rods and anaerobic bacterial counts were different between group 3 (mean(s.d.) 2·46(0·88)) and group 4 (0) ($P < 0{\cdot}05$). However, total bacterial growth in the ileum did not differ significantly between groups.
Conclusion: In this pancreatitis model, without biliary obstruction, bacterial overgrowth of the duodenum occurred, accompanied by BT. Colonic bacteria were predominantly involved. This model offers the possibility of studying the relationship between SBBO, BT and the pathogenesis of necrotic (infected) pancreatitis.

Dopamine attenuates neutrophil–endothelial interaction and is a putative anti-inflammatory cytokine

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Background: Activated neutrophil (PMN) adherence to vascular endothelium comprises a key step for both transendothelial migration and initiation of potentially deleterious release of PMN products. Previous work has shown that the biogenic amine dopamine (DA) functions as an anti-inflammatory cytokine by inducing PMN apoptosis. The effect of DA on PMN transendothelial migration and adhesion receptor expression as well as on the endothelial molecules, E-selectin and intercellular adhesion molecule (ICAM) 1, was evaluated.
Methods: PMNs were isolated from healthy controls, stimulated with lipopolysaccharide (LPS) and tumour necrosis factor (TNF) α and treated with DA. CD11b and CD18 PMN adhesion receptor expression was assessed flow cytometrically. In a separate transwell experiment, the effect of the chemoattractant peptide interleukin (IL) 8 on PMN migration was assessed. Human umbilical vein endothelial cells were stimulated with LPS/TNF-α, incubated with DA, and ICAM-1 and E-selectin endothelial molecule expression was assessed.
Results:

	Normal PMNs	Stimulated PMNs	Stimulated PMNs + DA 10 μmol l⁻¹	Stimulated PMNs + DA 100 μmol l⁻¹
PMN transendothelial migration (%)				
No IL-8	14(1)	40(15)*	8(0)*†	8(0)*†
IL-8	25(2)	65(16)*	18(2)*†	20(3)*†
Adhesion receptor expression on endothelial cells and PMNs				
E-selectin	3·9(0·4)	8·1(0·5)*	4·3(0·2)†	3·7(0·1)†
ICAM-1	3·8(0·2)	9·0(0·8)*	4·3(0·1)†	4·6(0·0)†
CD11b	77(2)	252(5)*	174(3)*†	175(4)*†
CD18	140(4)	352(5)*	266(4)*†	220(3)*†

Values are mean(s.d.). *$P < 0{\cdot}01$ *versus* normal PMNs, †$P < 0{\cdot}05$ *versus* stimulated PMNs (analysis of variance)

There was a significant increase in transendothelial migration in stimulated PMNs as well as in CD11b/CD18, endothelial E-selectin and ICAM-1 expression compared with normal PMNs. DA attenuated these changes. The chemoattractant effect of IL-8 was also abolished.

Conclusion: These results show that DA attenuates the initial interaction between PMNs and endothelium, providing further evidence that it also functions as an anti-inflammatory cytokine.

Prospective randomized trial demonstrates that postoperative administration of glycyl-glutamine alleviates the reduction in human leucocyte antigen DR expression on human monocytes induced by surgery

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Background: The surface expression of major histocompatibility complex class II antigens (human leucocyte antigen (HLA) DR) on monocytes is a major indicator of the immunocompetence of these cells. Surgery, trauma and inflammation lead to a reduction in HLA-DR expression on monocytes, which is associated with an increased susceptibility to infection and sepsis. The authors have shown surface expression of HLA-DR on human monocytes *in vitro*. Following trauma or surgery, glutamine synthesis and secretion from skeletal muscle is increased; intracellular concentrations of glutamine, however, are significantly decreased. It was therefore hypothesized that postoperative infusion of glutamine dipeptides might prevent the decrease in HLA-DR expression on monocytes.

Methods: Thirty patients undergoing major abdominal surgery were allocated randomly to receive either 1500 ml Vamin (an amino acid solution containing no glutamine) (controls) or an isonitrogenic formulation containing Vamin and glycyl-glutamine (35 g glutamine) (GLY-GLN) or Vamin and alanyl-glutamine (35 g glutamine) (ALA-GLN) as a continuous infusion over 48 h after operation. The operations performed included oesophagectomy (three), gastrectomy (four), partial pancreatoduodenectomy (ten), hemihepatectomy (one) and drainage surgery of the biliary/pancreatic duct (ten). Immediately after the operation and 48 h later blood samples were collected for determination of HLA-DR expression of monocytes *in vitro* by flow cytometry.

Results: The groups were comparable with respect to age, sex distribution and operating time. In the GLY-GLN group mean HLA-DR expression of monocytes at 48 h was significantly better preserved than in controls.

		HLA-DR (MCF)		
Group	n	Postop.	48 h	% postop.
Controls	10	21·0(3)	8·4(1)	42·5(4)
ALA-GLN	10	19·7(3)	9·1(3)	46·5(12)
GLY-GLN	10	19·2(3)	12·0(2)	65·0(7)*

Values are mean(s.e.m.). MCF, mean channel fluorescence. *$P = 0{\cdot}04$ *versus* control (Kruskal–Wallis test)

Conclusion: Postoperative infusion of GLY-GLN alleviates the immunosuppression induced by surgery. GLY-GLN may be superior to ALA-GLN because of the distinct immunological effect of glycine and alanine. The observed GLY-GLN-specific preservation of HLA-DR on monocytes following surgery may contribute to the prevention of infectious complications in patients undergoing major abdominal surgery.

Dietary glycine decreases liver injury after haemorrhagic shock in rats

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Background: Resuscitation from haemorrhagic shock induces profound changes in the physiological processes of the liver and activates inflammatory cascades that include activation of stress transcriptional factors and upregulation of tumour necrosis factor (TNF) synthesis. This process is accompanied by increased levels of free radicals that may contribute to acute organ damage. Intravenous administration of glycine, a simple amino acid, has been reported to decrease release of TNF and to improve the survival rate of rats after haemorrhagic shock or endotoxin administration. The effects of feeding a glycine-containing diet (5 per cent) on liver injury and on the oxidant–antioxidant balance in resuscitated haemorrhagic rats has been investigated.

Methods: Rats were bled to maintain mean arterial pressure at 30–35 mmHg for 1 h and subsequently resuscitated with 60 per cent shed blood and lactate Ringer's solution. Thiobarbituric acid reactive substances (TBARS) and the oxidized : reduced glutathione (GSSG : GSH) ratio were measured as markers of oxidative stresss. The activities of the antioxidant enzymes superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (Cat) were determined in liver cytosol.

Results: Levels of aspartate aminotransferase (ASAT) were increased 22-fold and levels of alanine aminotransferase (ALAT) eightfold 20 h after resuscitation. Leucocyte infiltration and pericentral necrosis were also observed. Serum nitrite concentration increased by 69 per cent. Liver TBARS increased by 32 per cent and the GSSG:GSH ratio by 106 per cent. There was a significant reduction in total liver glutathione concentration (−42 per cent) and in the activities of SOD (−23 per cent), GPx (−26 per cent) and Cat (−46 per cent). Serum nitrite, liver TBARS concentration and the antioxidant enzyme activities remained unchanged in animals receiving dietary glycine. The GSSG:GSH ratio and total glutathione concentration did not significantly differ from control values. The increase in serum ASAT and ALAT levels and in hepatic necrosis were markedly reduced.

Conclusion: Dietary glycine prevents liver injury caused by haemorrhagic shock in the rat. Diminished availability of nitric oxide and maintenance of the oxidant–antioxidant balance may reduce the pathophysiological sequelae of severe haemorrhage.

Postoperative septic complications and neoplastic progression in colorectal cancer

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Background: Proinflammatory cytokines, mainly interleukin (IL) 6, may induce suppressive effects on antitumour immunity. IL-6 inhibits T lymphocyte proliferation and maturation of dendritic cells. In the postoperative period, an increase in IL-6 serum level due to surgical trauma is a normal finding. Very high levels of IL-6 are detected only in patients with septic complications. In consideration of the suppressive effects of IL-6 on antitumour immunity, septic complications may promote a worsening of the late prognosis of patients undergoing radical treatment for cancer. To detect a possible negative effect on cancer progression due to sepsis after colorectal surgery, this study was carried out in patients who underwent radical surgery (Dukes' B and C stages). Cancer-related late recurrence and mortality rates were compared in patients with and without postoperative septic complications.

Methods: Patients who underwent operation for colorectal cancer between January 1987 and December 1998 were studied. Patients treated by emergency surgery, patients aged over 80 years, those with a previous or second neoplasm and patients treated with steroid therapy or other immunomodulatory drugs were excluded. Major surgical postoperative septic complications were considered: wall and intra-abdominal abscess and anastomotic leakage. Five-year survival (Kaplan–Meier curve) and recurrence rates were recorded.

Results: Some 210 patients were studied; 137 patients with a mean age of 65 (range 22–80) years and median follow-up of more than 5 years (range 12–144 months) had Dukes' B disease (77 men and 60 women). Of these 137 patients, 28 (20 per cent) had septic complications. Thirteen of 28 patients with sepsis had progression of cancer disease compared with 26 of 109 without sepsis ($P < 0.03$). In patients with sepsis the 5-year mortality rate was 32 per cent (nine of 28), worse than that in patients without sepsis (19 per cent; 21 of 109). Seventy-three patients (41 men and 32 women), of mean age 64 (range 38–80) years, with median follow-up greater than 5 years (range 13–120 months), had Dukes' C lesions. Of these 73 patients, 16 (22 per cent) had septic complications. Thirteen of 16 patients with sepsis had progression of cancer disease compared with 33 of 57 without sepsis. In those with sepsis the 5-year mortality rate was 75 per cent (12 of 16), significantly worse than that in patients without sepsis (40 per cent; 23 of 57) ($P < 0.02$).

Conclusion: The immunological response against cancer is generally impaired after major surgery owing to lymphocytopenia and lack of dendritic cells. It is known that IL-6 promotes suppression of antitumour-specific (dendritic cells and CD8 cytotoxic cells) and aspecific (IL-2 activation of lymphokine-activated killer cells) systems. The increase in IL-6 levels after surgery is relevant in patients with septic complications and this phenomenon may negatively influence the immunological control of malignant spread. As hypothesized, septic complications after radical surgery for colorectal cancer were followed by an increased recurrence rate in patients with both Dukes' B and C tumours. This finding supports a significant role for the immune system in the control of malignant progression of disease. The postoperative course represents a vulnerable period since septic complications and secondary immunosuppression negatively influence a cancer-related prognosis.

Impact of relaparotomy in patients with abdominal sepsis

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Background: This study determined whether relaparotomy has a positive or negative effect on prognostic scoring systems.

Methods: Between April 1995 and January 1997, 46 patients with abdominal sepsis were treated. The diagnosis of abdominal sepsis was defined as meeting the Bone criteria for sepsis before operation, in combination with infection of the abdomen proven by laparotomy. After the first laparotomy there were 41 relaparotomies in these 46 patients. From 2 days before to 3 days after the relaparotomy, data were collected to compile the Acute Physiology And Chronic Health Evaluation (APACHE) III and Multiple Organ Failure (MOF) scores. The scores were compared before and after relaparotomy, and were also compared between patients who had a recurrent infection in the abdomen and those who did not.

Results: During 41 relaparotomies, 16 patients were found to have a pus collection. Of these clinical infections only 11 had a positive culture. Overall the APACHE III and MOF scores were not significantly different before and after operation. In

patients with clinical infection there was also no difference pre and post operative. The same applied for patients with and without positive intraabdominal cultures.
Conclusion: Relaparotomy in patients with abdominal sepsis did not have a negative effect on prognosis within a few days after reoperation. The authors did not find any reason to use APACHE III or MOF scoring as an indication for relaparotomy.

Risk factors for nosocomial infection after elective pulmonary thoracic surgery

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Background: The aim was to identify risk factors for the development of infection after pulmonary surgery.
Methods: A retrospective analysis of 440 consecutive patients operated on between August 1987 and July 1997 was conducted.
Results: Nosocomial infections (NIs) were observed in 122 patients (27·7 per cent): pneumonia in 75 (17·0 per cent), urinary tract infection (UTI) in 40 (9·1 per cent), surgical site infection (SSI) in 37 (8·4 per cent), nine of which were pleural empyemas (2·0 per cent), and other infections in six (1·4 per cent). The infection-related mortality rate was 3·2 per cent (14 patients). Multivariate analysis of 21 variables revealed that the following were independent predictors for the development of NI:

Infection	COPD†	Alcoholism†	Haemoglobin $< 10\,\mathrm{g\,dl^{-1}}$‡	Cardiac disease	Diabetes†
Pneumonia	0·04	0·03	0·015	n.s.	n.s.
UTI	n.s.	n.s.	n.s.	n.s.	n.s.
SSI	n.s.	n.s.	n.s.	n.s.	0·002
Empyema	n.s.	n.s.	0·0005	n.s.	n.s.
Other	n.s.	n.s.	0·01	n.s.	n.s.
Total	n.s.	n.s.	n.s.	0·02	n.s.

COPD, chronic obstructive pulmonary disease; n.s., not significant.
†Four-field χ^2 test; ‡k*f-field χ^2 test

No operation-related factor, such as infection, indication for surgery, extension of pulmonary resection, duration of operation or transfusion requirements, had a significant influence on the development of NI.
Conclusion: The results indicate that impairment of the patient's ability to respond to surgical trauma is more important for the development of postoperative infection than factors related to the operation.

Decreased incidence of ventilator-associated pneumonia caused by *Pseudomonas aeruginosa* over 3 years

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Background: Ventilator-associated pneumonia (VAP) is a frequently occurring infection among critically ill patients. *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Escherichia coli* are the most common micro-organisms causing VAP. The aim of this study was to ascertain the incidence of VAP diagnosed with bronchoalveolar lavage (BAL) by these possible pathogenic micro-organisms (PPMOs). Because VAP is often preceded by colonization of the oropharynx with the causative pathogen, sputum cultures were compared with the BAL cultures.
Methods: Over a 3-year period, all ventilated patients in two intensive care units ($n = 1136$) were reviewed for pneumonia. A VAP was present when the bacterial count of the BAL was more than 10^4 colony-forming units $\mathrm{ml^{-1}}$. The microbial results of all patients with a VAP (polymicrobial or monomicrobial) were recorded.
Results: The mean incidence of VAP was 8 per cent ($n = 92$), decreasing only slightly during the period ($P > 0{\cdot}05$). The most frequent aetiological agents were *P. aeruginosa* ($n = 34$), *S. aureus* ($n = 22$), *E. coli* ($n = 16$) and *K. pneumoniae* ($n = 10$). The percentage of VAPs due to *P. aeruginosa* has declined progressively from 53 to 31 per cent. Concurrently, the incidence of *Pseudomonas* colonizing the sputum culture has declined (from 54 to 44 per cent). On the other hand, the incidence of VAP due to *E. coli* has increased from 13 ($n = 2$) to 36 per cent ($n = 6$). Colonization of the sputum with *E. coli* has similarly increased (from 13 to 27 per cent).
Conclusion: The incidence of VAP in the intensive care unit is in accordance with the literature, when diagnosed with strict criteria. No significant change in the incidence of VAP was noted during the 3-year period. Neither the decrease in incidence of VAP caused by *P. aeruginosa* nor the increase in *E. coli* pneumonia can be explained by a change in antibiotic regimens in the period studied. Hypothetically, cross-colonization of PPMOs by healthcare personnel can be influenced by hand-washing and wearing gloves. This can especially influence colonization by *P. aeruginosa*, thus explaining the decrease.

Procalcitonin plasma level as a marker of systemic infection in surgical patients in the intensive care unit

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Background: Increased (more than 0·5 ng $\mathrm{ml^{-1}}$) extrathyroidal production of procalcitonin (PCT; the prodromal molecule of calcitonin) has been proven to characterize cases of systemic bacterial infection. The aim of the present study was to investigate the possible role of PCT as an infection marker in 59 febrile surgical patients in the intensive care unit who were under several antimicrobial regimens.
Methods: PCT values were calculated every other day during the whole duration of the febrile period using the immunochemiluminescence method (Brahms Diagnostica, Berlin, Germany). A subgroup of ten patients (three with multiple

trauma, seven with an intra-abdominal site of infection) were considered to have sepsis (SS) because of their positive blood cultures (two Gram positive, eight Gram negative). A total of 30 patients presented with the systemic inflammatory response syndrome (SIRS), which was considered to have a septic aetiology in nine (four with peritonitis, one with pancreatitis and four with multiple trauma) (white blood cell count greater than 25 000 μl^{-1}, temperature above 39·5°C). Of the remaining patients, seven had an intra-abdominal abscess (IA) with various causes, six had acute non-complicated pancreatitis (AP) and six had localized burns (LB) (13·5–25 per cent of the total body surface).

Results: PCT values on the first day of fever (asymmetrical underlying distribution) are shown in the *Table*.

		SIRS				
	SS	All patients	Septic origin	IA	AP	LB
PCT ($ng\,ml^{-1}$)	8·1 (2·8–81·7)	2·5 (0·1–55)	5·0 (0·6–55)	1·4 (0–7·3)	0·4 (0·1–1·3)	0·3 (0·1–0·9)

Values are median (range)

Conclusion: (1) Increased PCT levels are the hallmark of sepsis even from the first day of its appearance as opposed to cases of localized infection. (2) PCT levels are increased in cases of SIRS of infectious origin. (3) Low PCT levels (less than 1 $ng\,ml^{-1}$) in patients with pancreatitis are indicative of an uncomplicated evolution. (4) Unexpectedly high PCT levels should be taken into consideration for the choice of optimal antimicrobial regimen.

Impaired *ex vivo* lipopolysaccharide-stimulated whole blood tumour necrosis factor production may identify patients in the intensive care unit with 'sepsis' and multiple system organ failure

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Background: There is currently no reliable diagnostic test to identify patients with sepsis in the intensive care unit (ICU) or patients with multiple system organ failure (MSOF). It was previously found that *in vitro* pretreatment of monocytes with lipopolysaccharide (LPS) induced blunted tumour necrosis factor (TNF) release to LPS rechallenge. It was hypothesized that patients exposed to LPS or septic stimuli *in vivo* would produce less TNF when stimulated *ex vivo* with LPS. This preliminary study sought to determine whether impaired *ex vivo* TNF release was associated with measurable differences in clinical outcome.

Methods: Heparinized whole blood was obtained from 27 ICU patients and five healthy controls, and incubated immediately with or without LPS 10 $ng\,ml^{-1}$ at 37°C for 3 h, then centrifuged to recover serum. Serum TNF levels were measured using an enzyme-linked immunosorbent assay and expressed as mean(s.e.m.). Clinical data, such as ICU length of stay (LOS), duration of mechanical ventilation, white blood cell count and positive cultures, were obtained retrospectively. Quartiles (I, 0–25 per cent; II, 26–50 per cent; III, 51–75 per cent; and IV, 76–100 per cent) were identified on the basis of the distribution of plotted LPS-stimulated whole blood TNF values. Statistical analysis was by χ^2 and Student's *t* tests.

Results: A wide range of LPS-stimulated whole blood TNF production was observed in ICU patients (5·1(0·7) $ng\,ml^{-1}$) and controls (6·6(1·0) $ng\,ml^{-1}$). Patients identified in the lowest quartile ($n = 6$) of TNF producers (less than 2 $ng\,ml^{-1}$) had significantly lower TNF production and a higher incidence of infection (83 *versus* 38 per cent), and longer LOS (21·8 *versus* 9·0 days) and duration of mechanical ventilation (18·3 *versus* 6·0 days) than patients in quartiles II–IV ($n = 21$). Patients in the lowest quartile had significantly lower TNF production (1·1(0·2) $ng\,ml^{-1}$) than normal controls (6·6(1·0) $ng\,ml^{-1}$) ($P < 0·05$) or ICU patients in any other quartile (quartile II: 2·9(0·2) $ng\,ml^{-1}$, quartile III: 5·3(0·3) $ng\,ml^{-1}$, quartile IV: 10·4(1·3) $ng\,ml^{-1}$) ($P < 0·05$).

Conclusion: The lowest levels of *ex vivo* LPS-stimulated whole blood TNF production were associated with a prolonged ICU stay, a higher incidence of positive cultures and a prolonged need for mechanical ventilation. Impaired TNF release may be a manifestation of monocyte endotoxin tolerance and may be a marker of monocytic dysfunction. Determination of whole blood *ex vivo* LPS-stimulated TNF production could be useful in the diagnosis of severe sepsis and MSOF in patients in the ICU.

Evidence of a prognostic value for platelet surface antigen expression in severe abdominal sepsis

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Background: There is evidence for the involvement of platelets under septic conditions. Alterations of platelet surface antigen expression at the onset of septic shock have been reported previously. The aim of this study was to investigate platelet activation as well as changes in platelet receptors during the course of severe sepsis.

Methods: The study population included six patients with severe sepsis because of peritonitis or necrotizing pancreatitis. Platelet investigations were performed daily. For analysis three characteristic time points during the course were defined restrospectively (A, onset of septic shock; B, significant clinical improvement; C, last sample before death). A double-colour flow cytometric assay was performed in whole blood to determine platelet surface expression of CD63, CD62P, CD42B, CD36 and CD31.

Results: At the onset of septic shock (A) all patients showed similar antigen expression (CD63, 1·24; CD62P, 0·59; CD42B, 30·9; CD36, 28·0; CD31, 18·2). In surviving patients (B, $n = 2$) antigen expression was lower (CD63, 0·70; CD62P, 0·38; CD42B, 27·8; CD31, 12·4) or higher (CD36, 27·6) than in patients (C, $n = 4$) who died (CD63, 1·55; CD62P, 0·72; CD42B, 36·5; CD36, 24·1; CD31, 21·1).

Conclusion: Although the study population was very small and heterogeneous, these results point to a correlation of platelet surface antigen expression with clinical outcome (survival). It is hypothesized that platelet surface antigen expression, reflecting platelet activation, might be a predictive factor in the course of severe sepsis.

Hepatitis B virus transmission from a surgeon to patients during high-risk as well as low-risk procedures: unnoticed transmissions over a 4-year period

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Background: Three cases of reported acute hepatitis B virus (HBV) led to the identification of a chronically HBV-infected surgeon, with a high viral load, who was a non-responder after vaccination.

Methods: A retrospective cohort study was conducted on 1564 patients operated on by this surgeon over a 4-year period.

Results Forty-nine patients (3·1 per cent) were positive for HBV markers. Based on HBV DNA sequencing and epidemiological data, transmission from the surgeon was confirmed in eight, probable in two, possible in 18 and excluded in 21 patients. One case of secondary transmission was identified from a patient to his wife, who died, presumably from fulminant hepatitis. A case–control study identified the duration of operation, the potential risk of the surgical procedure and the occurrence of complications during or after surgery as significant risk factors for HBV infection. At least eight of the 28 patients were infected during low-risk procedures.

Conclusion: Transmission from surgeons to patients at a low rate can remain unnoticed for a long period of time. Prevention requires a more stringent strategy for vaccination and testing of surgeons. It also requires revision of policies allowing HBV-infected surgeons to perform presumed 'low-risk' procedures.

Influence of antibiotic prophylaxis on perioperative risk in traumatology with the new concept of clinic modelling randomized trials in animals

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Background: Surgical outcome depends not only on different therapies, but also on different additionally applied measures like prophylaxis (antibiotics, heparin, etc.) and their complex interaction. The aim of this study was to establish a new concept of clinic modelling randomized trials (CMRTs) in rats (haemorrhagic shock model) to investigate the harmful or beneficial effects of antibiotic prophylaxis in trauma patients (evidence-based medicine). Elements of the clinical scenario and methodology of randomized trials were modelled as accurately as possible in this CMRT.

Methods: Conditions of the rat model (CMRT) were adapted to the methodology of clinical trials and the clinical scenario with respect to sample size calculation, blinding and randomized allocation in a two-block design ($n = 20$ animals per group), anaesthesia with fentanyl–droperidol, standardized operation (soft tissue damage, tibia fracture and nailing), antibiotic prophylaxis 1 h before operation (intravenous cefuroxime 20 mg kg^{-1} *versus* placebo (sodium chloride)), volume substitution (Ringer) and postoperative analgesia. The clinical situation of healthy (American Society of Anesthesiologists (ASA) grade I and II) and severely injured (ASA III and IV) patients was simulated in the CMRT by sham operation and preoperative blood-letting, respectively, to initiate a relevant shock (1·5 h of mean arterial pressure 50 mmHg, blood pressure measured in the femoral artery). The shock period was followed by resuscitation (volume loading) with Ringer solution 40 ml kg^{-1}. The endpoint was the 21-day mortality rate. Fracture healing was documented by radiography.

Results: The animal model was established successfully. The required blood-letting for relevant shock was 20 ml kg^{-1}. The mortality rate in animals without blood-letting simulating healthy patients (ASA I and II) was zero in the cefuroxime and in placebo groups ($n = 20$ per group). In the experiment with preoperative blood-letting (ASA III and IV, $n = 20$ per group) a clear but not significant trend in the mortality rate for the cefuroxime group (20 per cent) *versus* placebo (40 per cent) could be observed (1 d.f., $P > 0·05$, χ^2 test). Disturbances of fracture healing did not occur.

Conclusion: The clinical impact (evidence based) of antibiotic prophylaxis in traumatology was demonstrated in these experiments. The influence of other currently used antibiotics in trauma patients could be investigated in such animal models (CMRTs) instead of expensive and time-consuming clinical trials. The results of this study suggest the advantage of prophylaxis with cefuroxime in severely injured patients. Other antibiotics and the pathophysiological mechanisms will be investigated in further studies.

'Components separation technique': a useful method for repair of (contaminated) abdominal wall defects

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Background: Since 1994 the 'components separation technique' has been used for the repair of large abdominal wall defects, thus avoiding the use of prosthetic material.
Methods: The results of the method were evaluated retrospectively in 40 patients. There were ten women and 30 men, of mean age 50·3 years and mean body mass index 27·4 kg m^{-2}. All had midline hernias that could not be closed primarily. Hernias occurred in 25 patients after acute surgery of whom 11 had open treatment of generalized peritonitis. Reconstruction was performed under clean conditions in 27 patients, clean contaminated in seven and contaminated or dirty in six. In 13 patients the reconstruction was combined with bowel surgery.
Results: The postoperative course was complicated in 15 patients: one case of wound dehiscence, five haematomas, two seromas, six wound infections and one case of respiratory insufficiency. One patient died 6 days after operation from mesenteric thrombosis. After a mean follow-up of 8·5 (range 0–20) months recurrent hernias were found in eight patients. One patient had an enterocutaneous fistula in a newly created umbilicus. All recurrences appeared after clean operations.
Conclusion: The 'components separation technique' is useful for the reconstruction of large abdominal wall defects, especially under contaminated conditions where the use of prosthetic material is contraindicated. Moreover the technique can be used to close the abdomen at an early stage after open treatment of peritonitis. Devascularization of the skin and a large wound surface created by mobilization of the skin and subcutis are major drawbacks. Release of the external oblique muscle via separate skin incisions can prevent these problems and makes the method applicable for patients with an enterostomy.

Adaptation of the vacuum-assisted closure system for laparostomy

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Background: Laparostomy is a useful treatment option in selective cases of severe peritonitis. However, owing to the size, massive secretion and intestinal fistulas, the granulation of this wound is a long and troublesome process.
Methods: From 1994 to 1999 the vacuum-assisted closure (VAC) system has been used as the wound dressing for laparostomies.
Results: The VAC system has the following advantages compared with conventional dressings: (1) efficient drainage of the wound; (2) rapid induction of a macroscopically healthy granulation; (3) little irritation of the surrounding skin; (4) possibility of kinetic therapy in patients with acute respiratory distress syndrome; and (5) less psychological distress of the patient, owing to the closed dressing of an otherwise massively secreting wound. The major side-effect observed was erosion-induced bleeding. Bleeding always ceased after a pause of the VAC system for 24 h. The major complication of the system was clogging by fibrinous secretions and thickened intestinal fluids. These occlusions could be prevented by adding a rinsing line with 0·9 per cent sodium chloride. Interestingly, there was no increase in bacterial colonization of the abdomen.
Conclusion: Owing to multiple variables in patients with laparostomy an objective assessment of the advantages of VAC treatment compared with conventional dressings is almost impossible. However, it appears that the VAC system is a rational approach for the treatment of these large wound surfaces.

Antivascular endothelial growth factor therapy prevents peritoneal adhesion formation without adversely affecting wound strength or anastomotic integrity

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Background: Postoperative intra-abdominal adhesion formation remains a significant cause of complications in surgical patients. To date, no agent has been shown consistently to block adhesion formation; preliminary evidence has shown that intra-abdominal adhesion formation is angiogenesis dependent. Vascular endothelial growth factor (VEGF) is a potent stimulator of angiogenesis and promotes vascular leakage. This study determined whether a specific VEGF monoclonal antibody (mAb) could prevent postoperative adhesion formation without affecting wound and anastomotic integrity.
Methods: After developing a standardized peritoneal injury which resulted in a reproducible adhesion model, 40 CD-1 mice were randomized and treated intraperitoneally with either VEGF mAb ($n = 20$) or immunoglobulin (Ig) G isotype control mAb ($n = 20$) at the time of abdominal closure. Animals ($n = 10$ per group) were killed on postoperative day 14, and the development of intra-abdominal adhesions was determined and graded blindly using well established criteria. Animals ($n = 10$ per group) were also killed 10 days after operation, and laparotomy wounds and gastrointestinal anastomoses were assessed by tensiometry. Statistical analyses were performed using the Mann–Whitney and Fisher's exact tests.
Results:

	Adhesion score				Wound breaking strength (N)	
	0	1	2	3	Laparotomy wound	Gastrointestinal anastomosis
VEGF mAb	8	1	1	0	0·89(0·18)	0·68(0·12)
IgG mAb	0	1	3	6	0·92(0·25)	0·71(0·14)

Values are mean(s.d.)

Treatment with VEGF mAb resulted in a significantly lower incidence of adhesion formation compared with control animals ($P < 0.001$). Furthermore, intergroup analysis for the presence of marked adhesions (grade 2 or 3) demonstrated that mice treated with VEGF mAb had a significantly lower incidence of advanced adhesions compared with controls (10 *versus* 90 per cent). Laparotomy wound and gastrointestinal anastomotic strength were similar between groups.

Conclusion: This study demonstrates that the formation of postoperative intra-abdominal adhesions is attenuated following the administration of VEGF mAb without adversely affecting wound strength or anastomotic integrity.

Intra-abdominal bacterial growth and detection of bacteria by fluorescence *in situ* hybridization in patients with secondary peritonitis

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Background: Patients with secondary peritonitis are treated by surgery and intravenous antibiotics depending on the micro-organisms cultured from abdominal fluid samples. However, such samples may not be representative of the origin of the intra-abdominal infection. Therefore, this study determined (1) whether different micro-organisms are cultured from abdominal fluid, peritoneum and blood samples, and (2) whether fluorescence *in situ* hybridization (FISH), with 16S ribosomal RNA-targeted probes applied on peritoneum samples, is more efficient than standard culturing techniques.
Methods: In a pilot study, samples of abdominal fluid, peritoneum and blood were obtained from two groups of patients: six patients with secondary peritonitis (peritonitis group) and five patients without peritonitis (control group).
Results: Standard culturing techniques revealed coagulase-negative staphylococci (CNS) and yeast in abdominal fluid samples in three of six patients; *Escherichia coli*, enterococci, CNS and *Citrobacter* in peritoneum samples in five of six patients; and no micro-organisms in the blood samples from the peritonitis group. In the control group, CNS were cultured from the abdominal fluid samples in one of five patients, while no micro-organisms were cultured from peritoneum samples and CNS were cultured from the blood samples in one of five patients. The FISH technique revealed a large number of various anaerobic bacteria in peritoneum samples in one of six patients in the peritonitis group. In the control group no bacteria were detected.
Conclusion: Micro-organisms cultured from abdominal fluid differ from those cultured from peritoneum samples. The FISH technique confirmed these findings in only one case. However, it is a promising technique for the identification and localization of bacteria causing secondary peritonitis.

Surgical treatment of infected pancreatic necrosis

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Background: Twenty-six cases of infected pancreatic necrosis (IPN) treated by means of operation in the years 1997–1999 are presented.
Methods: The diagnosis of IPN was established before surgery by means of contrast-enhanced computed tomography and fine-needle aspiration of the infected pancreatic and peripancreatic tissue. Microbiological findings of infected tissue most commonly showed *Escherichia coli* (12) and *Klebsiella pneumoniae* (eight). Candidiasis was observed in three cases. All patients were stratified according to Acute Physiology And Chronic Health Evaluation (APACHE) II score within 24 h of admission to the ward and before planned surgery. Wide surgical exploration of the omental sac and retroperitoneal space, gentle necrosectomy of necrotic tissue, and continuous omental sac lavage in connection with an 'open abdomen' technique was carried out within 4–22 (mean 10) days from the onset of the disease. Planned relaparotomies were performed every 4–5 days until all the necrotic tissue was removed and granulation of the operating area was observed. Closure of the abdomen was performed within 14–34 (mean 23) days after primary laparotomy.
Results: Six patients died (mortality rate 23 per cent) during the postoperative period from multisystem organ failure accompanying septic shock. The poor outcome was related to a high APACHE II score (11–15). During the postoperative period the following complications were observed: respiratory insufficiency requiring mechanical ventilation (24 cases), colonic fistula (five), pancreatic fistula (three), renal insufficiency requiring haemofiltration (three), upper gastrointestinal bleeding (two) and gastric fistula (one). Incisional hernia developed in five patients who left hospital. The hospital stay for survivors ranged between 26 and 52 (mean 36) days.
Conclusion: Diagnosis of IPN based on dynamic computed tomography and bacteriological examination of necrotic aspirate and the consecutive surgical treatment, including wide repeated necrosectomy and continuous lavage combined with an 'open abdomen' technique, is the management of choice, and may improve the results of treatment.

Sterile pancreatic necrosis is not a clinical entity

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Background: The question of whether to operate or not in patients with sterile pancreatic necrosis (SPN) is controversial. The basis for this discussion has been the assumption that SPN represents a clinical entity. The aim of the present study was to question this hypothesis.

Methods: All patients with SPN diagnosed by contrast-enhanced computed tomography and negative bacterial cultures were included in the study. A retrospective analysis of prospectively collected data, including organ function, Acute Physiology And Chronic Health Evaluation (APACHE) II scores, duration of intensive care therapy and hospitalization, and death, was performed.
Results: From 1990 to 1999, 43 patients were treated for SPN. All patients had to undergo intensive care therapy. There were two clearly different types of patient: (1) a group of 20 patients with less severe disease treated successfully without operation and (2) 23 patients with progressive organ dysfunction despite intensive care, who had to undergo surgery. The rates of organ dysfunction (18 *versus* 100 per cent), median APACHE II scores (7 *versus* 17), mortality rate (zero *versus* 26 per cent), duration of intensive care (9 *versus* 23 days) and hospital stay (26 *versus* 45 days) were significantly different between the two groups.
Conclusion: According to this study SPN is not a clinical entity. Future discussions on therapeutic strategies should take this finding into consideration.

Chronic recurrent subareolar breast abscess: incidence and treatment

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Background: Chronic recurrent subareolar breast abscesses (SBAs) are a distinct entity of non-puerperal breast abscesses. They are located in the retroareolar or periareolar area and occur as a result of obstruction of the lactiferous ducts by squamous metaplasia. Unfamiliarity with this entity often leads to inadequate treatment, and recurrences frequently appear with extended fistulas. For this reason, the incidence of and the treatment for SBAs were analysed retrospectively.
Methods: In two clinics all patients with non-puerperal breast abscesses were analysed during a 6-year period.
Results: Some 98 patients were included (in the same period 35 patients were treated for puerperal breast abscesses). In 85 patients a total of 204 SBAs occurred (the largest study known). The remaining 13 patients had other non-puerperal breast abscesses such as cystic breast disease, inflammatory breast carcinoma and fat necrosis. If treatment of the SBA did not include excising the ductus lactiferus, the recurrence rate was 72 per cent. If the ductus lactiferus was excised, the recurrence rate was 37 per cent.
Conclusion: If a patient presents with a non-puerperal breast abscess in a subareolar location, the first diagnosis to consider should be (chronic recurrent) SBA. Smoking appears to be an important precipitating factor. In a recurrent SBA most frequently anaerobic micro-organisms are cultured. The primary treatment of SBA may comprise only incision and drainage. However, this should be followed by excision of the affected ductus lactiferus, including a part of the mamilla. If the affected ductus is not sufficiently excised, the SBA is destined to become a problematic chronic recurrent abscess.

Isolation of lysogenic staphylophage and its potential use as a treatment of methicillin-resistant *Staphylococcus aureus* surgical infections

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Background: The aim was to develop a new cost-effective, accessible method for treating multidrug-resistant bacterial infections in which the possibility for emergence of resistant strains is greatly reduced. Methicillin-resistant *Staphylococcus aureus* (MRSA) surgical wound infection was used as a model for these studies.
Methods: A collection of lysogenic bacteriophage was made by isolating *Staphylococcus*-specific bacteriophage (staphylophage) from clinical MRSA samples from England, Bulgaria and Poland. The phage was selected and characterized according to host range, source, morphology and stability. Resistance profiles of the *S. aureus* isolates (SAIs) for 16 antibiotics, including methicillin, were determined.
Results: Some 86 per cent of the SAIs were multidrug resistant. When the 152 SAIs were incubated with eight different *S. aureus* cultivating strains 79 per cent produced at least one phage able to infect at least one of the cultivating strains. 72·4 per cent were able to infect two or more.
Conclusion: Lysogenic MRSA isolates are a characterizable, widely available source of staphylophage that can be used as an alternative to the traditional environmental sources. A specific pattern for geographical distribution of lysogenic staphylophage has been demonstrated which further facilitates the isolation process. The narrow host range of bacteriophage compared with chemotherapeutic agents ensures a minimal effect on non-pathogenic bacteria within the patient. This is an ongoing study and these are preliminary results. At the end of the study a method for isolation and development of therapeutic phage will be available for use in the industrial and hospital setting.

Benchmarks and control charts for surgical site infections

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Background: Although benchmarks and control charts are basic quality improvement tools, few surgeons use them to monitor surgical site infection (SSI). Obstacles to widespread acceptance include: (1) small denominators, (2) complexities of adjusting for patient risk and (3) scepticism about their true purpose (cost cutting, surgical privilege determination or improving outcomes).
Methods: The application of benchmark charts (using US national SSI rates as limits) and control charts (using facility

rates as limits) was studied in 51 hospitals submitting data to the AICE National Database Initiative. SSI rates were risk adjusted by calculating a new statistic, the standardized infection ratio (SIR), based on the risk index suggested by the Centers for Disease Control National Nosocomial Infection Surveillance Study. Fourteen different types of control chart were examined and 115 suspiciously high or low monthly rates were flagged. Participating hospital epidemiologists investigated and classified each flag as 'a real problem' (potentially preventable) or 'not a problem' (beyond the control of personnel at this facility).

Results: None of the standard, widely recommended, control charts studied showed practical value for identifying either preventable rate increases or outbreaks (clusters due to a single organism). On the other hand, several types of risk-adjusted control chart based on the SIR correctly identified most true opportunities for improvement. Sensitivity, specificity and receiver–operator characteristic (ROC) analysis revealed that the XmR chart of monthly SIRs would be useful in hospitals with smaller surgical volumes (ROC area = 0·732, $P = 0{\cdot}001$). For larger hospitals, the most sensitive and robust SIR chart for real-time monitoring of surgical infections was the mXmR chart (ROC area = 0·753, $P = 0{\cdot}0005$).

Standardized infection ratio: the next generation of risk-adjusted wound infection measures

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Background: The scientific literature overwhelmingly supports the value of surgical site infection (SSI) surveillance with feedback of infection rates to surgeons. Recognizing that feedback has little value without some form of adjustment for patient factors, surgeons long ago developed the four-level wound classification system. In the 1980s the SENIC multivariate risk index was introduced, followed by the National Nosocomial Infection Surveillance multivariate risk index which is the currently recommended US standard.

Methods: To address recent advances in surgical technology, ambulatory surgery, and differences between the USA and other countries, newer risk-adjustment methods were explored. The ideal approach would overcome the following common practical problems encountered in generating SSI rates such as: (1) new patient-level risk factors, (2) technology-specific factors, (3) small monthly denominators and (4) postdischarge surveillance. Despite increased mathematical complexity, an acceptable risk-adjustment technique must still provide easily interpretable results.

Results: The standardized infection ratio (SIR) is proposed as the next generation in epidemiological approaches for monitoring and feeding back risk-adjusted SSI rates to surgeons. The SIR is a single monthly number for each surgeon, calculated by dividing the observed number of SSIs by the expected number predicted from a complex statistical model of patient-level and technology-specific risk factors. Like the well known standardized mortality ratio, the SIR offers the advantage of providing one generalizable quality index regardless of the mix of operations performed. In addition, the SIR is well suited to control chart techniques and for providing valid interhospital comparisons.

Conclusion: The SIR model offers simple data input and easily interpretable output suitable for application in all healthcare settings worldwide.

Surveillance of infections acquired in intensive care units in the Netherlands

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Background: The aim was to develop and implement standardized surveillance of infections acquired in the intensive care unit (ICU) in the PREZIES network of hospitals in the Netherlands.

Methods: Surveillance was standardized by protocol and uniform software. Patients were included if they stayed in the ICU for 48 h or more. Data were aggregated at the national level and analysed univariately.

Results: Standardized surveillance of infections acquired in the ICU was introduced in 22 (5 per cent) of hospitals in the Netherlands. Data on 990 patients from ten hospitals (July 1997 to September 1998) were available for analysis. Median length of stay was 6 days. The median Acute Physiology And Chronic Health Evaluation score was 18 and the median age 64 years. In total 256 patients became infected. Per 1000 patient days, 16·1 pneumonias, 3·7 cases of central vascular catheter-related sepsis and 11·1 urinary tract infections were found. Per 1000 patient days, patients were ventilated for 708 days, had a urinary catheter for 950 days and a central vascular catheter for 746 days. Selective contamination of the gastrointestinal tract was employed in 6 per cent and systemic antibiotics in 68 per cent of patients.

Conclusion: It is possible to conduct standardized surveillance of ICU-acquired infections. The data provide insight into the incidence of nosocomial infections in ICU patients in the Netherlands and can be used as reference values for participating hospitals.

Pilot surveillance in the Netherlands of sepsis related to central vascular catheters

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Background: The aim was to study the feasibility of surveillance of sepsis related to central vascular catheters (CVCs) in the PREZIES network of hospitals in the Netherlands.
Methods: A national expert team developed a surveillance protocol. Ten hospitals conducted the surveillance during 3 months in 1999. The plot was evaluated in an interview with the infection control practitioner (ICP) of each hospital and by analysing the data collected.
Results: ICPs considered this surveillance labour intensive and made recommendations on issues such as further clarifying the case definition and standardization of culturing of blood and catheters. Of 874 patients with one or more CVCs, 29 (3·3 per cent) had CVC sepsis. Most frequently infusion catheters were studied. Median length of stay was 5 days. Catheters in the femoral artery or vein, with more than one lumen, for parenteral feeding, or in place for more than 48 h were associated with CVC sepsis.
Conclusion: The surveillance of CVC sepsis in PREZIES hospitals is feasible and can generate useful reference values.

Dutch reference data on the incidence of surgical site infection

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Background: The PREZIES national surveillance network supports Dutch hospitals in introducing surveillance of surgical site infection (SSI), generates reference data on the incidence of SSI and associated risk factors, and provides an infrastructure for interventional research. Its ultimate goal is to reduce the occurrence of SSI. The aim was to discuss the methods and results of the national SSI surveillance.
Methods: The participating institutions developed a surveillance protocol and an agreement on participation and privacy aspects. For each patient under surveillance, infection control practitioners collected data on the type of procedure, the occurrence of a superficial and/or deep SSI, and on several risk factors, i.e. age, American Society of Anesthesiologists score, wound contamination class, duration of surgery, preoperative length of stay, use of antibiotic prophylaxis, multiple surgery and elective/emergency surgery. Hospitals received standardized feedback reports comparing their own SSI rates with the national reference. Validation and use of surveillance data were studied within subsets of hospitals.
Results: Since June 1996, 70 of 114 hospitals of all types and sizes participated. The *Table* shows the number of operations, the incidence of all SSIs, the use of prophylactic antibiotics and the number of participating hospitals for five commonly recorded procedures.

Procedure	*n*	All SSIs (%)	Antibiotic prophylaxis (% operations)	No. of hospitals
Total hip replacement	9147	2·9 (2·6–3·2)	96	49
Caesarean section	1474	2·4 (1·6–3·2)	57	15
Mastectomy	1368	6·1 (4·8–7·4)	6	26
Femoral head prosthesis	1355	6·8 (5·5–8·1)	96	38
Appendicectomy	940	5·0 (3·6–6·4)	60	15

Values in parentheses are 95 per cent confidence intervals

Of 38 hospitals studied, 19 used surveillance results in education, 22 in policy and decision making, and 16 in initiating interventions. Five reported a reduction in SSI incidence. A prevalence survey of SSI showed high agreement ($\kappa = 0{\cdot}88$) with the validating team.
Conclusion: The PREZIES network provides hospitals with good quality national reference data that are used to support their policy for prevention of SSI.

Role of tumour necrosis factor in lung injury caused by intestinal ischaemia–perfusion

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Background: Despite the well known inflammatory effects of tumour necrosis factor (TNF), the mechanism of TNF-mediated lung injury following ischaemia–reperfusion (IR) is still unclear. In this study, the role of TNF in the development of acute lung injury following intestinal IR was investigated.
Methods: Male Wistar rats underwent either sham operation ($n = 10$) or 1 h of superior mesenteric artery occlusion and 2 h of reperfusion (IR; $n = 10$) or pretreatment with anti-TNF polyclonal antibody 2 mg kg^{-1} and IR ($n = 6$). Lung injury was evaluated by Evans blue dye concentration, immunohistochemical staining and morphometric analysis. Intestinal injury was assessed by Evans blue dye concentration and histological examination.
Results: Intestinal IR resulted in lung injury characterized by an increase in Evans blue dye concentration, polymorphonuclear neutrophil (PMN) sequestration, and obvious staining for expression of pulmonary CD11b and CD18. Pretreatment of animals with anti-TNF antibodies led to a reduction in the sequestration of PMNs ($P < 0{\cdot}05$), a decrease in expression of pulmonary intercellular adhesion molecule 1 and CD18 ($P < 0{\cdot}01$), and a diminished histological grade compared with the IR-only group. Anti-TNF antibody pretreatment also reduced the intestinal microvascular injury after intestinal IR.
Conclusion: Treatment with an anti-TNF antibody resulted in significant attenuation of lung injury following intestinal IR, which is at least partially TNF mediated. The data indicate

that TNF is an important trigger for upregulation of pulmonary endothelial and neutrophil adhesion molecules after intestinal IR.

Moderate hypothermia prevents cell injury in rats with severe haemorrhagic shock

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Background: This study aimed to evaluate a possible protective and therapeutic effect of mild to moderate hypothermia in severe haemorrhagic shock. Brainstem is one of the most sensitive tissues to oxidative stress in the early phase of haemorrhagic shock. The haemorrhagic oxidative stress at various core temperatures was studied using reduced glutathione (GSH) levels and thiobarbituric acid reactive substances (TBARS) as markers of lipid peroxidation in brainstem homogenate.
Methods: Forty rats were divided into four groups, of which one constituted the non-bleeding normothermia control group. In all of the three study groups, the rats were bled to 40 per cent of their estimated blood volume while they were being held at normothermia, mild (32°C) or moderate (28°C) hypothermia. Mean arterial pressure, rectal temperature, heart and breathing rates were recorded during the procedures. After 1 h of shock, tissue samples were removed by craniectomy.
Results: The tissue levels of TBARS increased significantly in normothermic and mildly hypothermic haemorrhagic shock groups (10·74 and 8·26 nmol g^{-1}) compared with control (3·50 nmol g^{-1}) ($P < 0.001$). However, the tissue TBARS level in the moderately hypothermic group was only minimally increased (4·53 nmol g^{-1}). GSH levels fell slightly in normothermic and mildly hypothermic bleeding rats, and were unchanged in moderately hypothermic rats.
Conclusion: The TBARS level, which was a predictor of oxidant damage, changed slightly during severe haemorrhagic shock when the rats were moderately hypothermic. Hypothermia had a protective effect against cell injury during haemorrhagic shock. Tissue TBARS levels correlated well with the degree of tissue damage; lower levels suggested hypothermic protection.

Surgical and laboratory findings in children with neutropenic enteropathy

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Background: The term neutropenic enteropathy (NE) is used to describe inflammatory conditions of the gastrointestinal system in patients who receive chemotherapy for haematological malignancy. Although the initial treatment of choice in NE is non-operative, with bowel rest, decompression, nutritional support and broad-spectrum antibiotics, operative intervention is needed in patients with the advent of the disease. The surgical and laboratory findings of seven patients with NE who required surgical treatment are presented.
Methods: Patients' medical records were reviewed to obtain age, sex, diagnosis, laboratory findings with neutrophil counts, blood cultures and the surgical findings. The onset of neutropenia and the diagnosis of NE were recorded for each patient.
Results: There were four girls and three boys, with a mean age of 6 years (range 9 months to 16 years). The primary diseases were acute myelocytic leukaemia in two, acute lymphocytic leukaemia in one and lymphoma in four patients. In all but two patients, the neutrophil counts were less than 1000 mm^{-3}, with positive blood cultures at diagnosis. The onset of the NE was determined as mean(s.d.) 3(2) days after the onset of neutropenia. Haemorrhage, marked oedema, patchy inflammation and multiple adhesions of the bowel, perforation and localized abscess were the main operative findings. The lesions were mostly localized in the terminal ileum and the ascending colon. After resection of the affected segment of bowel, stomas (three) and end-to-end anastomoses (three) were performed. Primary repair of the perforation site was performed in one patient with gastric perforation. Four patients recovered with rapid resolution of neutropenia, while three patients with persistent neutropenia died.
Conclusion: A favourable outcome for patients with NE is related to early recognition of the intra-abdominal infection, appropriately timed surgical intervention and a prompt postoperative return of normal circulating levels of neutrophils.

Role of liver-produced prostaglandins in experimental intra-abdominal sepsis

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Background: While the cyclo-oxygenase (Cox) 1 pathway has physiological effects such as maintaining endothelial integrity, Cox-2 also has pathological effects. The role of liver-produced prostaglandins and their specificity were studied in an experimental sepsis model.
Methods: Some 28 male Wistar rats were divided into five groups. In all groups intra-abdominal sepsis was created by caecal ligation and puncture. Group 1 (IASG) comprised five rats and all had intra-abdominal sepsis only. In group 2 (MG; $n = 5$) all rats received meloxicam 5 mg kg^{-1}. Group 3 (NG; $n = 5$) received nimesulid 2 mg kg^{-1}. In group 4 (APG; $n = 5$) antiplatelet activating factor (PAF) agent was administered. Group 5 (MAPG) received meloxicam and anti-PAF. Following 24 h of intra-abdominal sepsis, all rats underwent reoperation. Peritonitis was confirmed pathologically and liver biopsies were performed. The levels of prostaglandin

(PG) E_2 and $PGF_{2\alpha}$ as prototypic end-products of the Cox-1 and -2 pathway were measured in the biopsy specimens.
Results: The mean $PGF_{2\alpha}$ levels were 539·2, 17·8, 194·4, 341·0 and 229·2 pg per mg liver tissue protein in groups 1–5 respectively. The respective mean PGE_2 levels were 422·6, 438·0, 272·6, 331·4 and 205 pg mg^{-1}. $PGF_{2\alpha}$ values in MG were significantly different from those in all other groups ($P < 0·001$), and those in NG and MAPG were different from those in IASG and APG. On the other hand, PGE_2 levels were significantly lower in NG, MAPG and APG than in IASG and MG. Liver tissue PAF was also detected in all groups except NG. Mean PAF levels in IASG, MG, APG and MAPG were 44·4, 33·2, 12·2 and 14·6 pg per mg tissue protein respectively.
Conclusion: (1) PAF is an important mediator in intra-abdominal sepsis. (2) Liver $PGF_{2\alpha}$ may play a role in intra-abdominal sepsis independently from PAF. (3) Anti-PAF agent alone may help healing in peritoneal sepsis, but the main therapeutic agents are $PGF_{2\alpha}$ blocking agents.

Cytokines and myeloperoxidase as markers of purulent-septic complications of acute pancreatitis

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Background: Purulent-septic complications often determine the outcome of severe acute pancreatitis. Unfortunately, there are no useful markers that can predict the contamination of necrotic foci.
Methods: Thirty-eight patients with severe pancreatitis were treated. The plasma levels of interleukin (IL) 1, IL-6, IL-8 and myeloperoxidase (MPO) were studied in all patients on days 1, 3, 7, 14 and 21 after the onset of acute pancreatitis.
Results: Raised levels of all inflammatory mediators were observed in all patients on the first day. A gradual decrease in cytokine and MPO levels was noted in patients with sterile necrosis and a favourable course of acute pancreatitis (17 patients). Contamination of the necrotic foci was accompanied by a rise in IL-8 (140·0 pg ml^{-1} or more) and MPO (11·0 nmol ml^{-1} or more) levels, which preceded the clinical manifestation of purulent complications. These results were confirmed by ultrasonographically guided aspiration. Two types of purulent-septic complications were identified: local and disseminating. Local purulent-septic complications (nine patients) were characterized by a moderate increase in cytokine levels and were associated with a good prognosis. The disseminating purulent-septic complications group (12 patients) was characterized by highest levels of proinflammatory cytokines, significant multiple organ failure and a poor prognosis. Eight patients with widespread purulent-septic complications died.
Conclusion: IL-8 and MPO plasma levels are valuable markers of infected necrosis in acute pancreatitis.

Abdominal tuberculosis in children

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Background: Abdominal tuberculosis (AT) is a rare cause of abdominal infection in children. Surgical intervention is rarely indicated, other than for obtaining a specimen for histopathological diagnosis or for the treatment of complications.
Methods: The medical records of 13 patients who were operated on with the diagnosis of AT, between 1983 and 1999, were reviewed retrospectively.
Results: The median age was 7 years (range 6 months to 10 years). The clinical signs and symptoms were as follows: abdominal pain (eight patients), loss of weight (seven), abdominal mass (six), vomiting (four) and night fever (four). Twelve patients were operated on, while diagnostic laparoscopy was perfomed in one. Patients operated on with the diagnosis of acute abdomen were diagnosed immediately at laparotomy. Surgery was limited to sampling of peritoneum and/or lymph node biopsy and ascites. The reason for surgical intervention was intestinal obstruction (eight), abdominal mass or ascites (six), psoas abscess (one) and intussusception (one). In all patients the diagnosis was confirmed by either histopathological or microbiological examination. In eight patients the AT was defined as intestinal and mesenteric type, in three patients it was localized to the peritoneum and in two the disease was diffuse. All patients were treated with INH, rifampicin and streptomycin–pyrazinamide combination. Two patients, one with a faecal fistula and one with malnutrition, came from another hospital. All patients survived and were treated successfully except the patient with a faecal fistula.
Conclusion: The diagnosis of AT is difficult before presentation with complications of intra-abdominal infection. In patients with suspected AT, aggressive surgery should be avoided and surgical intervention should be limited to tissue and/or fluid sampling.

Dexamethasone in hyperdynamic sepsis in children

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Background: A recent study analysed the usefulness of dexamethasone (DX) in hyperdynamic sepsis in children. This prospective study was performed in order to confirm or refute the conclusions obtained previously.
Methods: A prospective, randomized and sequential study was performed in 38 patients of both sexes with a mean age of 10 years. Patients had at least five of the following clinical features to be included in the study: hyperthermia, oliguria, tachycardia, tachypnoea, cyanosis or another sign of hypox-

aemia, impaired consciousness (confusion, meningeal signs, psychomotor excitation, delirium) and digestive disturbance (haemorrhage, vomiting, diarrhoea). Criteria for exclusion were: previous organ failure (adrenal or renal insufficiency), diabetes, tuberculosis, systemic mycosis, corticosteroid sensibility and immunodeficiency. Patients were divided into two equal groups: placebo control and DX, the latter with forward contribution to the dose of 3 mg kg^{-1} each time, repeated at 12 and 24 h. In all cases, clinic and laboratory variables used commonly in intensive care were monitored. The evaluations were immediately before, and at 48 and 72 h after, the first dose of DX.

Results: There was no significant difference between the two groups.

Conclusion: The application of macrodoses of DX in hyperdynamic sepsis in children is not indicated.

New approach in flow-cytometric determination of endotoxin during endotoxic shock

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Background: Serum endotoxin was formerly measured with the non-specific *Limulus* lysate assay. The present approach was to quantitate the amount of endotoxin bound by peripheral mononuclear cells in order to develop a method for the diagnosis of early septic shock.

Methods: Using a murine monoclonal antibody (WN1-222/5), which binds highly specifically to lipopolysaccharide (LPS), a new method for measuring the amount of LPS bound to peripheral mononuclear cells was developed. Ten pigs were studied under sedation and peripheral mononuclear cells were taken every 4 h to determine the concentration of endotoxin by flow cytometry. The results are shown in the *Table*.

Results:

	Time after LPS infusion (h)				
	0*	1	4	6	8
Marked cells (%)	32	61	75	72	85

The percentage of marked mononuclear cells increased during shock. Only in the last hours before death did the rate of increase decline.

Conclusion: Preliminary data on marked mononuclear cells showed that the amount of natural incorporated endotoxin, i.e. the quantity of bound endotoxin before infusion, was 32 per cent.

Microbiology of postoperative peritonitis

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Background: The microbiology of secondary peritonitis is well known and standards of antibiotic therapy are established. In contrast, little is known about the bacteriology of postoperative peritonitis. Resistant strains could be involved and patients may have had previous antibiotic treatment.

Methods: The intraoperative and postoperative bacteriology (10 days after operation) of all 88 cases of postoperative peritonitis occurring between September 1994 and May 1999 were documented. Resistances were used to determine effective antibiotic therapy.

Results: Compared with secondary peritonitis, enterococci outnumbered *Escherichia coli* in postoperative peritonitis. While *E. coli* showed no advanced resistance, the different pattern of bacterial findings (e.g. enterococci, *Enterobacter*, Gram-positive bacteria) leads to failures of standard therapy for secondary peritonitis. Imipenem–cilastatin failed in 20 per cent, piperacillin–tazobactam in 31, aminoglycosides in 31, ciprofloxacin in 37 and third-generation cephalosporins in 47 per cent (the latter three combined with metronidazole).

Conclusion: Cephalosporins, the 'gold standard' in secondary peritonitis, fail in postoperative cases. Carbapenems are the drugs of choice. Aminoglycosides should be avoided in these patients.

Macrophages that have ingested apoptotic neutrophils release tissue inhibitor of matrix metalloproteinase 1

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Background: Apoptosis of neutrophils (PMNs) *in vivo* is followed by their rapid uptake into adjacent phagocytic cells, a critical process in tissue remodelling, regulation of the immune response and resolution of inflammation. Tissue inhibitor of matrix metalloproteinase (TIMP) 1 is crucial in regulating the matrix-degrading properties of matrix metalloproteinases released by activated PMNs in inflammatory foci. The aim was to elucidate whether mononuclear-derived phagocytes (MDPs) release TIMP-1 and/or MMP-9 after phagocytosis of apoptotic PMNs.

Methods: MDPs were prepared from peripheral blood monocytes after isolation by culture in well plates for 7–10 days. PMNs were isolated from similarly healthy volunteers. PMN apoptosis was induced by 10 min of ultraviolet irradiation at 254 nm. After a further 6 h of incubation apoptosis was assessed and was routinely greater than 50 per cent. Apoptotic PMNs were then added to MDPs in specific ratios. After 1 h non-phagocytosed PMNs were washed away. RPMI was added to

MDPs in well plates and 18 h later the supernatant was collected. Phagocytosis of opsonized zymosan, exposure to tumour necrosis factor (TNF) α and lipopolysaccharide (LPS), and finally MDPs alone were used as controls. TIMP-1 was quantified by enzyme-linked immunosorbent assay.

Results: TIMP-1 was released by MDPs after phagocytosis of apoptotic PMNs and opsonized zymosan. MDPs also produced TIMP-1 after stimulation with TNF-α–LPS. Levels of TIMP-1 from these MDPs were significantly different from those in MDPs alone.

	Control MDPs 4×10^6 ml^{-1}	Apoptotic PMNs 5×10^6 ml^{-1}	Opsonized zymosan 5 mg ml^{-1}	TNF-α 10 ng ml^{-1} + LPS 25 ng ml^{-1}
TIMP-1 (ng ml^{-1})	0·2(1·0)	1·3(0·2)*	3·3(1·7)*	4·4(1·5)*

Values are mean(s.d.). *$P = 0{\cdot}0001$ (analysis of variance)

Conclusion: Phagocytosis of apoptotic PMNs is an integral part of the host's attempt to resolve inflammation in altered immune states such as the systemic inflammatory response syndrome in which PMNs persistently release proinflammatory substances damaging the local microenvironment. This study has demonstrated that MDPs release TIMP-1 after phagocytosis of apoptotic PMNs and that this may play a role in the regulation of tissue remodelling and repair in response to inflammation.

Bacterial lipoprotein induces endotoxin-independent tolerance to the systemic inflammatory response syndrome *in vivo* and *in vitro*

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Background: Sublethal doses of endotoxin (lipopolysaccharide; LPS) induce tolerance *in vivo* and *in vitro*, and protect against the lethal effects of a further LPS challenge. Tolerance is characterized by diminished production of tumour necrosis factor (TNF) α. Bacterial lipoprotein (BLP), another bacterial wall component, might induce tolerance against its own lethal effects as well as those of endotoxin.

Methods: Ninety male MF-1 mice (mean(s.d.) weight 18(2) g) were randomized into three groups ($n = 30$ per group). Mice in group 1 received a single BLP-tolerant dose (10 mg kg^{-1}) by intraperitoneal injection, whereas mice in group 2 received a second BLP-tolerant dose (10 mg kg^{-1}) after 24 h. Following induction of tolerance, all mice were challenged with high doses of LPS 45 mg kg^{-1}, BLP 45 mg kg^{-1} or a combination of LPS 30 mg kg^{-1} plus BLP 30 mg kg^{-1}. Mice in group 3 were treated with a high dose of the above agents only. Mortality was assessed at 24 and 48 h. Macrophages were isolated from mice and pretreated *in vitro* with culture medium alone or culture medium containing LPS 10 ng ml^{-1} or BLP 10 ng ml^{-1} for 24 h. The cells were then stimulated with high doses (100–1000 ng ml^{-1}) of LPS, BLP or LPS plus BLP for 6 h. The cell culture supernatants were collected and TNF-α levels were determined using enzyme-linked immunosorbent assay.

Results:

	Mortality rate					
	LPS 45 mg kg^{-1}		BLP 45 mg kg^{-1}		LPS 30 mg kg^{-1} + BLP 30 mg kg^{-1}	
	24 h	48 h	24 h	48 h	24 h	48 h
No tolerance	80	80	60	60	60	80
Single tolerance	40*	40*	0*	0*	0*	0*
Repeat tolerance	20*	30*	0*	0*	0*	0*

*$P < 0{\cdot}05$ *versus* mice without tolerance (log rank test)

BLP-induced tolerance significantly improved survival compared with that of mice without tolerance ($P < 0{\cdot}05$). *In vitro*, pretreatment of murine macrophages with BLP significantly attenuated LPS, BLP and LPS plus BLP stimulation-induced TNF-α production.

Conclusion: BLP mimics LPS in the development of the systemic inflammatory response syndrome. Furthermore, BLP is capable of inducing tolerance, both *in vivo* and *in vitro*, which subsequently prevents BLP- and LPS plus BLP-induced death.

Novel animal model of septic shock following smoke inhalation

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Background: The lesions of smoke inhalation often progress in the context of sepsis and other complications of the burn illness to a critical state consistent with acute respiratory distress syndrome (ARDS). The aim of this study was to develop a standardized and reproducible model of sepsis after smoke inhalation in sheep.

Methods: Merino ewes ($n = 21$) were surgically prepared for the study. Five to seven days later, animals received a tracheostomy and 48 breaths of cotton smoke. *Pseudomonas aeruginosa* was suspended in 30 ml saline, which contained $2–5 \times 10^{11}$ colony-forming units, and injected into the right lobe (20 ml) and into the left lobe (10 ml) using a bronchoscope. After the bacterial challenge, the animals were ventilated mechanically with 100 per cent oxygen. Body temperature, haemodynamic parameters, blood gas and blood culture were monitored for 48 h.

Results: The sheep showed a hyperkinetic response and fall in arterial partial pressure of oxygen similar to that seen in severe sepsis in humans. These changes were more severe than in animals with smoke inhalation alone (*Fig. 1*).

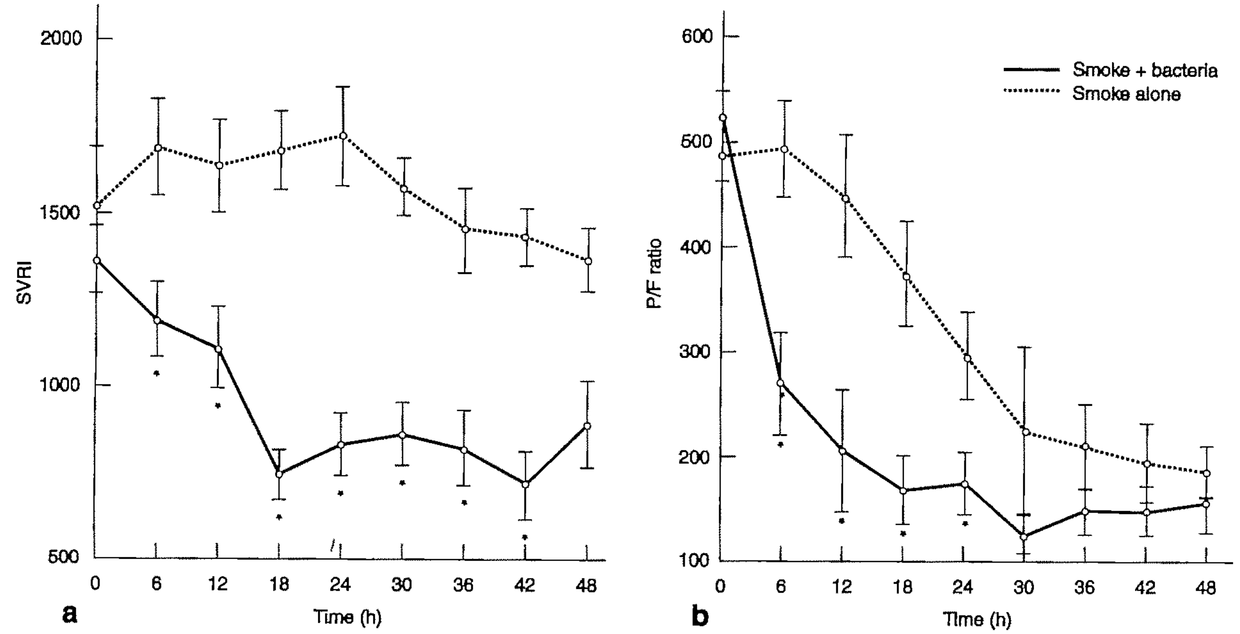

Fig. 1 Changes in systemic vascular resistance (SVRI) and P/F ratio in smoke alone ($n = 11$) and smoke plus bacteria ($n = 10$) groups. Values are mean(s.d.). $^*P < 0{\cdot}05$ *versus* smoke alone

Conclusion: This would be a good animal model of sepsis and ARDS.

Inflammatory response regulation by tacrolimus in an experimental model of multiorgan failure induced by bacterial translocation

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Background: Bacterial translocation may induce multiorgan failure (MF), an infrequent but very serious clinical situation. This study used the immunosuppressant tacrolimus to control the inflammatory response in order to avoid MF, and also aimed to elucidate its mode of action.

Methods: Male Wistar rats were divided into three groups: sham group, control MF group (zymosan intraperitoneal injection and studies at 2, 12 and 24 h) and tacrolimus group (different times of administration and studies at 2, 12 and 24 h). Survival, renal and hepatic function, microbiological cultures, neutrophil infiltration, oxygen free radicals, cytokines, cellular adhesion molecules and intracellular transcriptional mechanisms were studied in both renal and hepatic tissue.

Results: Use of tacrolimus before the systemic inflammatory response regulated this response (less production of free radicals, $P < 0{\cdot}01$; of cytokines, $P < 0{\cdot}01$; of neutrophil infiltration, $P < 0{\cdot}05$) by control of nuclear factor κB activation which induces minor expression of cellular adhesion molecules and minor production of the inflammatory mediators controlled by κB.

Conclusion: The use of prophylactic antiflammatory therapy in MF may be useful and tacrolimus has been demonstrated to be a powerful regulator of this situation.

Effects of systemic and intraperitoneal chemotherapy on bacterial translocation and peritoneal defence mechanisms

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Background: The aim of this study was to evaluate the effects of intraperitoneal and systemic chemotherapy on peritoneal defence mechanisms and bacterial translocation.

Methods: Four groups of adult male Wistar Albino rats ($n = 10$) were used in the study. The groups consisted of intraperitoneal chemotherapy (5-fluorouracil 20 mg kg^{-1} day^{-1} for 3 days), systemic chemotherapy (5-fluorouracil 20 mg kg^{-1} day^{-1} for 3 days) and their controls (systemic and intraperitoneal isotonic saline solution). Eight hours after the last dose of chemotherapy 10 ml sodium caseinate was applied intraperitoneally and 16 h later laparotomy was done under sterile conditions. During laparotomy 10 ml phosphate-buffered saline was applied and approximately 8 ml of this solution was collected. Phagocytic activity, bactericidal activity, peritoneal total cell numbers and morphology, peripheral blood leucocyte count and bacterial translocation were studied in this peritoneal solution. Tissue samples of mesenteric lymph node, liver, spleen and caecum were taken and homogenized for culturing.

Statistical analyses were done with Student's *t* test for independent samples.
Results: In the systemic chemotherapy group phagocytic activity (36 *versus* 52 per cent in control) and bactericidal activity (decreased in seven *versus* two in control) were significantly decreased. Peripheral and peritoneal leucocyte numbers were also decreased in the systemic chemotherapy group. Peritoneal cell morphology was not affected. Bacterial translocation occurred in mesenteric lymph nodes of five rats in this group. Intraperitoneal chemotherapy significantly decreased the phagocytic activity (33 *versus* 56 per cent in control). Peripheral and peritoneal leucocyte numbers were also decreased but the bactericidal activity and peritoneal cell morphology were not affected. In contrast to the systemic chemotherapy group, bacterial translocation was not detected.
Conclusion: Systemic chemotherapy caused bacterial translocation. Both systemic and intraperitoneal chemotherapy have detrimental effects on peritoneal defence mechanisms under experimental conditions.

Transforming growth factor β-mediated inhibition of src kinases is regulated by SHP-1

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Background: Transforming growth factor (TGF) β has been shown to suppress T cell effector functions. Although the mechanisms of such T cell suppression are not known, a disuption of the balance between protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs) has been implicated. The present study investigated the roles of the src-related PTKs, $P59^{fyn}$ and $P56^{lck}$, and the PTPs SHP-1 and SHP-2 in TGF-β-mediated T cell suppression.
Methods: Splenic T cells from rats were pretreated with TGF-β 25 ng ml^{-1} and subsequently stimulated with either anti-CD3 or anti-CD3 plus pervanadate (a PTP inhibitor). After incubation with specific antibodies and immunoprecipitation, the kinase activity of the PTKs was assessed by *in vitro* kinase assay. Phosphorylation of the PTPs was assessed using antiphosphotyrosine antibodies and immunoblotting.
Results: Incubation of T cells with TGF-β resulted in decreased activity of $P59^{fyn}$ and $P56^{lck}$. Although TGF-β treatment resulted in a concomitant increase in SHP-1 activity, no change in SHP-2 activity was observed. When T cells were stimulated with anti-CD3 in the presence of pervanadate, the TGF-β-mediated decrease in $P59^{fyn}$ and $P56^{lck}$ activity was completely prevented.
Conclusion: These findings show that TGF-β treatment of T cells results in suppression of src kinases, and suggests that such inhibition of kinase activity is mediated by upregulation of SHP-1.

Endothelins and carbon monoxide interact to regulate rat liver microcirculation after haemorrhagic shock

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Background: Upregulation of stress-induced vascular mediators such as endothelin (ET) 1, nitric oxide synthase (NOS)–nitric oxide or the haem oxygenase (HO)–carbon monoxide pathway may contribute to altered microvascular responsiveness after ischaemia and reperfusion. A profound induction of HO-1 and an increase in portal resistance after blockade of the HO pathway has been shown to occur after haemorrhagic shock and resuscitation (H/R). This study investigated whether the observed increased portal resistance after blockade of the HO pathway was mediated by a concomitant upregulation of ET-l.
Methods: Sprague–Dawley rats ($n = 10$ per group) were subjected to H/R (mean arterial pressure 40 mmHg for 1 h, followed by 5 h of resuscitation). Expression of HO-1, inducible NOS (iNOS) and ET-1 was studied by standard Northern blot analysis and reverse transcriptase–polymerase chain reaction. At 6 h either the ET antagonist bosentan 10 mg kg^{-1} or vehicle was injected. After 10 min the HO pathway was blocked in all animals by tin protoporphyrin (SnPP) IX 50 µmol kg^{-1}. Subsequently portal flow and portal pressure or sinusoidal liver blood flow (assessed by intravital epifluorescence microscopy) were measured for 30 min.
Results: A profound induction in ET-1 paralleled induced HO-1 messenger RNA (mRNA) gene expression after H/R (ET-1, mean(s.d.) 9·0(1·1)-fold; HO-1, 5·9(0·3)-fold induction at 6 h); iNOS mRNA was below the detection limit. Blockade of the HO pathway led to a significant peak increase in the portal vein resistance (ΔPVR; $P < 0·05$). There was a trend to a lower peak increase after administration of bosentan ($P = 0·07$) (ΔPVR: sham SnPP-IX, 0·17(0·05) mmHg min ml^{-1}; shock vehicle SnPP-IX, 0·57(0·15) mmHg min ml^{-1}; shock bosentan SnPP-IX, 0·29(0·05) mmHg min ml^{-1}). Regarding liver microcirculation, pretreatment with bosentan significantly attenuated the observed decrease in perfused sinusoids (PS) and in perfusion index (PI) after blockade of the HO pathway (shock vehicle SnPP-IX: PS 23·1(1·1) mm^{-1}, PI 1000(134) µm^3 s^{-1} mm^{-1}; shock bosentan SnPP-IX: PS 28·8(1·8) mm^{-1}, PI 1483(159) µm^3 s^{-1} mm^{-1}; $P < 0·05$).
Conclusion: These results suggest a functional interaction of the unregulated vasodilator carbon monoxide and the vasoconstrictor ET-1 at the sinusoidal level in rat liver after H/R.

Elective total hip replacement surgery may be a poor model of the inflammatory response to trauma

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Background: One of the many problems associated with studying the inflammatory response to major trauma is the variability of injuries and their severity. To overcome this problem, an assessment was made of whether elective total hip replacement (THR) surgery, which includes skeletal and muscle trauma, might provide a reliable model of the inflammatory response to trauma.

Methods: Serial venous blood samples were taken from ten patients before, during and for 24 h after THR. Sandwich immunoassays were performed to detect free and receptor-bound interleukin (IL) 6 and tumour necrosis factor (TNF) α. Whole blood was also taken from nine of the patients for *in vitro* incubation with endotoxin to assess white cell responsiveness.

Results: None of the patients had a measurable TNF-α response during or after surgery. Only two patients had raised IL-6 during and after surgery (maximum 145 pg ml^{-1}). Incubation of preoperative blood samples with endotoxin resulted in TNF-α and IL-6 production. The median for TNF-α was 710 (range 416–2800) pg ml^{-1} and that for IL-6 was 1050 (range 121–2350) pg ml^{-1}. Some 24 h after surgery the median for TNF-α was only 450 (range 75–1760) pg ml^{-1}. The median IL-6 production was 950 (range 124–1840) pg ml^{-1}. There was a reduction in *in vitro* TNF-α production in all nine patients (mean reduction 57 per cent; $P < 0{\cdot}05$) at 24 h. There was no significant change in *in vitro* IL-6 production before and after surgery. The reduction in TNF-α response indicated downregulation, which was not apparent for IL-6.

Conclusion: In this study THR did not produce the typical inflammatory response described for other forms of elective surgery. THR may not be a reliable model for studying the inflammatory response to trauma. The cement used to secure the prosthesis may have an effect on the inflammatory response.

Hypertonic saline–dextran is ineffective for resuscitation after thoracic blast and haemorrhage

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Background: Small-volume resuscitation using hypertonic solutions is increasing in popularity for the treatment of hypovolaemia. However, its effect in the blast casualty is unknown. The present study compared the effects of resuscitation with hypertonic saline–dextran with those of whole blood and colloid (Haemaccel) in an experimental model of blast injury and haemorrhage.

Methods: Male Wistar rats (235–264 g body-weight) were used in three groups of six animals anaesthetized with intravenous alphadolone–alphaxalone 19–21 mg kg^{-1} h^{-1}. Heart period (HP) was measured from the electrocardiogram and mean arterial blood pressure (MBP) via the tail artery. Body temperature was maintained at 38·0°C. At the end of the study the animals were killed with an overdose of anaesthetic. Each group received a blast wave focused on the ventral thorax. Some 10 min after the blast all groups received a haemorrhage of 40 per cent total estimated blood volume (BV, 6·06 mg kg^{-1}) at 2 per cent BV min^{-1}.

Results: Blast (group 1) induced a significant bradycardia (HP increasing to mean(s.e.m.) 543(64) ms from 155(4) ms; $P < 0{\cdot}05$, analysis of variance) and hypotension (fall in MBP to 35(3) mmHg from 106(4) mmHg). Thereafter there was partial recovery before subsequent haemorrhage significantly reduced MBP to 26(3) mmHg and increased HP to 189(15) ms. The response in groups 2 and 3 was not significantly different from that in group 1. Some 20 min later resuscitation with 40 per cent prehaemorrhage blood volume using autologous blood (group 1) or colloid (group 2) restored MBP to 113(7) and 98(2) mmHg respectively. The effects of blood and colloid were maintained for the remaining 30 min of the study. Although resuscitation with 7·5 per cent saline–6 per cent dextran 70 (4 ml kg^{-1}) in group 3 increased MBP to 92(5) mmHg initially, it fell significantly within 5 min, reaching 43(5) mmHg 30 min after resuscitation. This was associated with a significant tachycardia (HP 127(4) ms), which was not seen in the other groups.

Conclusion: These data provide no support for the use of hypertonic saline–dextran in resuscitation following blast and haemorrhage.

Luminal endotoxin modifies reaction to gut ischaemia–reperfusion injury in the pig

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Background: Translocation of bacteria and their products through the intestinal mucosa during ischaemia–reperfusion (I/R) may contribute to gut I/R injury.

Methods: In order to study the role of luminal endotoxin in gut I/R injury, two groups of seven germ-free pigs each were studied by clamping of the superior mesenteric artery, with and without luminal administration of endotoxin. Two control groups of seven germ-free pigs, with and without endotoxin, were not clamped. Translocation of an inert indicator (polyethyleneglycol (PEG) 3350), mucosal ischaemia (measured by tonometry) and haemodynamics were assessed.

Results: Both clamped groups showed ischaemic injury as measured by raised PEG 3350 urinary levels, lowered intestinal pH, and increased intramucosal arterial and intramucosal portal partial pressure of carbon dioxide gradients. Luminal endotoxin application did not aggravate this I/R injury, nor did it influence haemodynamics. The PEG 3350 level in the clamped endotoxin group was significantly lower than that in the clamped control group (mean(s.d.) 0·55(0·37) *versus* 1·82(0·70); $P = 0{\cdot}001$), suggesting a blunting influence of endotoxin on the I/R injury. This might be explained by a desensitizing effect on leucocytes in the gut wall by luminal endotoxin before clamping and diminishing the I/R-induced production of cytokines in the gut wall.

Conclusion: Endotoxin does not significantly mediate gut I/R injury in the pig and might desensitize the gut wall leucocytes, resulting in decreased translocation of large molecules, including bacterial products and endotoxin.

Two-hit model of haemorrhagic shock and *Pseudomonas* sepsis

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Background: Shock or trauma is a frequent prerequisite of bacterial sepsis. This has not, however, been reported in connection with related animal models. Therefore a porcine two-hit model was established with haemorrhage and resuscitation followed by the induction of sepsis with *Pseudomonas aeruginosa*.

Methods: Thirteen pigs were anaesthetized and permanently catheterized. Seven were subjected to haemorrhagic shock (bleeding until a mean of 50 per cent of the estimated blood volume remained) for 45 min, and then resuscitated with crystalloid, colloid and shed blood. A further six animals without shock served as controls. All pigs were fully conscious. The following day a continuous intravenous infusion of *P. aeruginosa* ($1{\cdot}6 \times 10^7$ colony-forming units $\text{kg}^{-1}\,\text{h}^{-1}$) was given for 24 h, followed by a reduced dose ($1{\cdot}6 \times 10^6$ colony-forming units $\text{kg}^{-1}\,\text{h}^{-1}$) for a further 24 h. The animals were then observed for another 48 h.

Results: All animals fulfilled the criteria for sepsis. However, the initial fever, arterial pressure and systemic vascular resistance were significantly lower in the shock group. In contrast, the pulmonary pressure, pulmonary vascular resistance and cardiac index were raised ($P < 0{\cdot}05$, shock *versus* control group).

Conclusion: These data indicate that sepsis is aggravated by a preceding haemorrhagic shock. This two-hit model considers one important precondition of human sepsis and may contribute to the development of a better treatment for this condition.

Fluid shifts during cardiopulmonary bypass with special reference to the effects of hypothermia

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Background: Generalized overhydration, oedema and organ dysfunction occurs in patients undergoing open heart surgery using cardiopulmonary bypass (CPB) and hypothermia. Inflammatory reactions induced by contact between blood and the foreign surfaces of the extracorporeal circuit are commonly held responsible for the disturbances in fluid balance ('capillary leak syndrome'). Using the CPB circuit reservoir as a fluid gauge (measuring continuous extracorporeal blood volume), fluid shifts between the intravascular and the extravascular space, and differences between normothermic and moderately hypothermic CPB, were examined.

Methods: Piglets were placed on CPB (thoracotomy) under general anaesthesia. In the normothermic group ($n = 7$) the core temperature was kept at 38°C before and during 2 h on CPB, whereas in the hypothermic group ($n = 7$) the temperature was lowered to 29°C during bypass. In addition to accurate recording of fluid during operation, the extracorporeal blood volume was kept constant by maintaining a certain blood level in the CPB circuit's reservoir. Acetated Ringer was used as priming solution in the CPB, as maintenance fluid and for adding fluid to the reservoir if necessary.

Results: Cardiac output, serum electrolytes and arterial blood gases were all similar in the two groups. Haematocrit fell significantly following the start of CPB in both groups. The reservoir fluid level fell markedly in both groups necessitating fluid supplementation. This extra fluid requirement was transient in the normothermic group, but persisted in hypothermic animals. At the end of 2 h of CPB the hypothermic animals had received seven times more extra fluid than the normothermic pigs.

Conclusion: There were strong indications of a greater fluid extravasation induced by hypothermia. The model described, using the PBC circuit reservoir as a fluid gauge, provides the opportunity for further study of fluid volume shifts, their causes and potential ways to manipulate fluid pathophysiology related to hypothermia and to PBC.

Blockade of Kupffer cells by gadolinium chloride or dichloromethylene diphosphonate influences hepatic microcirculation after sepsis and haemorrhagic shock

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Background: The liver plays a key role in the host defence response after haemorrhagic shock–resuscitation (H/R) and sepsis. Kupffer cells (KCs) have been shown to be a trigger and motor of the subsequent inflammatory response syndrome. This may lead to hepatocellular dysfunction, microcirculatory alterations and liver injury involving, for example, tumour necrosis factor α, interleukin (IL) 1 and IL-6. In a double-blind study the effect of KC blockade with either gadolinium chloride or liposome-entrapped dichloromethylene diphosphonate (DMD) on hepatic microvascular flow after H/R and sepsis was investigated.

Methods: After pretreatment with intravenous gadolinium chloride 10 mg kg^{-1}, DMD 1 mg kg^{-1} or saline 24 h before induction of shock, male Sprague-Dawley rats ($n = 6$–10 per group and time) were subjected to either haemorrhagic shock (mean arterial pressure 40 mmHg) for 60 min followed by resuscitation or lipopolysaccharide (LPS) 1 mg kg^{-1} intravenously. Microvascular flow was assessed by intravital microscopy of fluorescence-marked leucocytes in liver sinusoids at baseline, and 1, 6 and 12 h after shock induction.

Results: In saline groups, the mean(s.d.) leucocyte flow was significantly ($P < 0{\cdot}05$) higher at 1 h (20 759(2901) $\mu m^3 s^{-1}$) and 6 h (16 278(2916) $\mu m^3 s^{-1}$) after H/R as well as at 6 h after LPS (17 661(3949) $\mu m^3 s^{-1}$) compared with the baseline value (13 509(1580) $\mu m^3 s^{-1}$). Animals pretreated with gadolinium chloride showed a significant flow increase compared with baseline (11 797(1124) $\mu m^3 s^{-1}$) at 1 h following H/R (26 269(5909) $\mu m^3 s^{-1}$). In DMD-pretreated animals leucocyte flow showed no significant change over time, following either H/R or LPS treatment. However, flow was significantly higher at baseline (18 054(998) $\mu m^3 s^{-1}$) *versus* gadolinium chloride and saline groups. In addition, DMD-treated animals showed higher flow values 1 h after LPS challenge (20 665(2337) μm^3 s^{-1}) compared with gadolinium chloride (13 110(1224) μm^3 s^{-1}) and saline (15 311(800) μm^3 s^{-1}) groups. Similarly, at 12 h after H/R the DMD group (21 782(1887) $\mu m^3 s^{-1}$) had higher flow values than the gadolinium chloride (14 026(1616) $\mu m^3 s^{-1}$) and saline (15 999(3175) $\mu m^3 s^{-1}$) groups.

Conclusion: These results imply a significant influence of KCs on regulation of microvascular perfusion in liver sinusoids under normal conditions as well as after H/R and sepsis. The data indicate differential pathways and effects of blocking KCs by gadolinium chloride and DMD.

Alteration of inflammatory response following small-volume resuscitation

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Background: Small-volume resuscitation is rather effective in the primary volume treatment of major trauma. Blood pressure stabilizing effects occur immediately but last for a limited period only. Influences on inflammatory reactions in humans have not been reported so far. This prospective randomized study therefore analysed the inflammatory response in the very early (pre)clinical period after administration of crystalloids plus starch, hyperosmolar/hyperoncotic starch and lyophilized plasma solutions.

Methods: Upon approval of the ethics committee, 41 patients were enrolled with multiple injuries (injury severity score (ISS) mean 34 (range 9–75)). The patients received randomly either standard solutions, i.e. starch plus crystalloids (group C (control); $n = 14$), hyperosmolar/hyperoncotic starch (group S (small volume); $n = 14$) or lyophilized plasma (group L (lyoplasma); $n = 13$). Subsets were performed according to the different solutions as well as to the severity of trauma (ISS below 17, 18–31, 32 or more) and survivors/non-survivors. The first blood sample was obtained at the scene of the accident before cardiopulmonary resuscitation, when appropriate. Subsequently, blood samples were collected hourly. All samples were spun immediately at 4°C and stored at −70°C. Interleukin (IL) 6 as well as several different prostaglandins (PGI_2, thromboxane A_2, PGE_2) were determined to characterize the overall inflammatory response.

Results: Eleven casualties (seven men and four women, mean age 31 years) died because of major trauma within 24 h after the incident. In all patients IL-6 levels promptly increased within the first 2 h, most pronounced in patients with the severest trauma (ISS greater than 32) and non-survivors. Patients in groups C and S had a comparable time course of IL-6 plasma levels with a slightly higher release in minor injuries (ISS less than 30). The same was true for prostaglandins. In contrast, patients in group L had clearly higher IL-6 concentrations during the first 2–12 h, again most pronounced in those with the severest trauma (ISS greater than 32).

Conclusion: These results demonstrate that the early systemic inflammatory response after small-volume resuscitation is rather similar to that of patients infused with standard-volume therapy after trauma. In contrast, lyoplasma seems to increase the inflammatory response regardless of the injury severity.

Cytokine induction by non-lipopolysaccharide components of *Neisseria meningitidis*

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Background: Lipopolysaccharide (LPS), or endotoxin, is considered responsible for the pattern of cytokine activation and the subsequent pathophysiological events during Gram-negative septic shock. To determine whether non-LPS components of *Neisseria meningitidis* are able to induce cytokine activation, the cytokine-inducing capacities of serogroup B wild-type *N. meningitidis* H44/76, of an LPS-deficient mutant (Plak 33) and of meningococcal LPS in human peripheral blood mononuclear cells were studied.

Methods: 2-Keto-3-deoxyoctanate spectrophotometry was used to obtain a molar-based quantitative comparison between LPS and bacteria.

Results: Whole meningococci H44/76 were more potent inducers of cytokine production than isolated LPS; the LPS-deficient meningococci, Plak 33, were also able to induce cytokine production. LPS-deficient meningococci supplemented with an amount of LPS equivalent to that present in the wild-type strain produced the same amount of cytokines as the wild-type meningococcus.

Conclusion: LPS is not the sole toxic element in meningococcal sepsis, because non-LPS components of *N. meningitidis* are able to induce cytokine activation substantially. Antiendotoxin therapy alone may not be sufficient to inhibit the pattern of cytokine activation and the subsequent pathophysiological events during meningococcal septic shock.

Determination of 2-keto-3-deoxyoctanate: a simple method for the quantitative comparison of cytokine induction by meningococcal lipopolysaccharide and that of other bacteria

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Background: Lipopolysaccharide (LPS), or endotoxin, is considered to be the toxic element in Gram-negative septic shock. There is increasing evidence that the pathogenic properties of LPS differ from species to species but, to date, exact comparison between the biological activities of LPS has been difficult.
Methods: With the aim of quantitatively comparing the cytokine-inducing capacities of *Neisseria meningitidis* LPS and *Escherichia coli* LPS in human peripheral blood mononuclear cells on a molar basis, 2-keto-3-deoxyoctanate (KDO) spectrophotometry was used.
Results: Since the KDO region of LPS is a preserved part of the LPS molecule, unlike the saccharide tail, and the molecular weight of this region is known, KDO measurement can provide accurate information about the molarity of an LPS suspension. On a molar basis, the cytokine-inducing capacity of meningococcal LPS was at least ten times higher than that of *E. coli* LPS.
Conclusion: KDO spectrophotometry is a simple method of making a quantitative comparison between the biological effects of different endotoxins. *N. meningitidis* LPS is a more potent inducer of cytokine production than *E. coli* LPS. This may, in part, explain the more fulminant course of meningococcal sepsis compared with *E. coli* sepsis.

Macrophage migration inhibitory factor as a counter-regulatory mediator of cortisol during septic shock

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Background: Migration inhibitory factor (MIF) is a widely expressed protein that is secreted in response to inflammatory or hormonal stimuli. MIF is both an endocrine hormone and immunological mediator that counter-regulates glucocorticoid (GC) action. The anti-inflammatory and immunosuppressive properties of GC are often beneficial but host homeostasis requires counter-regulatory systems for which MIF has been proposed.
Methods: Using a time-resolved fluorometric immunoasssay to detect serum MIF levels in patients with septic shock or multitrauma, the relation of MIF to cortisol and adrenocorticotrophic hormone (ACTH) was studied. Serum MIF, cortisol and ACTH were measured serially over 14 days in patients with septic shock ($n = 28$) and multitrauma ($n = 5$), and in healthy controls ($n = 41$). Haemodynamics, Acute Physiology And Chronic Health Evaluation II scores and intensive care unit deaths were also recorded.
Results: MIF levels were raised significantly on day 1 in septic shock (mean(s.d.) 12·5(3·7) ng ml^{-1}) compared with trauma (3·1(1·7) ng ml^{-1}) and controls (2·5(2·1) ng ml^{-1}). The time course of both MIF and cortisol showed persistently high levels in sepsis, independent of shock reversal or haemodynamics. Non-survivors had higher MIF levels than survivors from septic shock ($P < 0·05$). Regression analysis showed a significant correlation between MIF and cortisol levels ($r = 0·72$), but no correlation was found between MIF and other variables.
Conclusion: Increased serum MIF levels occurred in septic shock compared with trauma and controls. In septic shock a clear correlation was found between MIF and cortisol levels, suggesting a parallel increase of MIF with cortisol and indicating a counter-regulatory activity of MIF to dampen the protective effects of GC. Non-survivors had higher MIF levels at most time points, indicating that MIF might be a potential prognostic marker in septic shock.

Shape and propagation of systemic pulsatile blood pressure during the evolution of porcine haemorrhagic shock

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Background: The shape and propagation of systemic pulsatile blood pressure was evaluated during the evolution of haemorrhagic shock in pigs.
Methods: Twenty-seven Saffan anaesthetized, mechanically ventilated pigs were randomized to a control group, a haemorrhage group with no resuscitation (25 per cent blood loss over 20 min) and an identical haemorrhage group but with reinfusion of shed blood over a further 20 min. Standard invasive haemodynamic monitoring was conducted, as well as digital recordings of blood pressure (via semiconductor catheter-tipped pressure transducers) at consecutive sites from the aortic arch to the femoral artery.
Results: The data are presented as time-averaged isobaric pulsatile contour plots of wave propagation from the aortic arch to the femoral artery. The colour contours encompass relative pressure measurements from the troughs of diastole (blue) to the peaks of systole (red). Distance from aortic arch to femoral artery was 50 cm in this series and the time axis travelled from left to right and over 0·7 s for each figure. Data were obtained before and after 25% haemorrhage and again after restoration of blood volume.
Conclusion: The time-domain morphology of the pulsatile blood pressure waveform and its systemic propagation is changed during a survivable haemorrhage. Furthermore, recovery is apparent following blood volume restoration.

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double spacing

Prospective audit following the introduction of short-course preoperative radiotherapy for rectal cancer

Sir

We read with interest the paper by Lele *et al.* (*Br J Surg* 2000; **87**: 97–9) reporting the outcome following preoperative short-course radiotherapy. We have prospectively audited the outcome of the first 50 consecutive patients with rectal cancer offered short-course preoperative radiotherapy in Plymouth. The outcome in our series was very similar to that in North Trent (*Table 1*). We did not experience any problem with delay in treatment. The median time from referral to radiotherapy was 5 (range 1–14) days, and from radiotherapy to surgery a median of 5 (range 2–9) days.

We agree that short-course preoperative radiotherapy should be carefully audited or introduced as part of the CRO7 trial.

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Table 1 Outcome data

Plymouth	North Trent	
	(*n* = 50)	(*n* = 100)
Stoma/non-stoma	18 of 32	54 of 46
Dukes A:B:C ratio	7:18:25	11:45:44
Operative mortality rate (%)	0	3
Anastomotic leak	4 of 32	7 of 39
Perineal wound infection	3 of 15	9 of 49

Sir

We read with interest the article by Lele *et al.* examining preoperative short-course radiotherapy but feel their interpretation may represent an overly negative view. They demonstrated an increased complication rate in patients treated with radiotherapy, particularly regarding anastomotic leak rate.

Survival following treatment for rectal carcinoma remains only moderate and as there is always variability between surgeons[1] the cumulative probability of tumour-free survival at 5 years was 94% for Dukes A tumours, 87% for Dukes B, and 58% for Dukes C[2]. The patient group selected for radiotherapy is likely to represent low tumours, as demonstrated by the high proportion of abdominoperineal resections, and so the incidence of anastomotic leaks is likely to be higher. However, the whole point of these patients receiving adjuvant treatment is because they are at higher risk of recurrence with low tumours[3] and the potential to reduce this risk may justify an increase in complications. Do the leaks reported represent a clinical or radiological leak rate as most patients are likely to be defunctioned with a low anastomosis? Did a leak only delay closure of the stoma?

We have given preoperative short-course radiotherapy in combination with total mesorectal excision to all patients with resectable rectal carcinoma since June 1996 and have not demonstrated a significant increase in complications. We agree that this combination should be investigated further within controlled trials or audited series, but the potential of improving outcome for higher risk patients may justify a degree of increased morbidity.

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1 McArdle CS, Hole D. Impact of variability among surgeons on postoperative morbidity and mortality and ultimate survival [see comments]. *BMJ* 1991; **302**: 1501–5.
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Randomized clinical trial of topical phenylephrine in the treatment of faecal incontinence

Sir

We read with interest the article by Carapeti *et al.* (*Br J Surg* 2000; **87**: 38–42) describing the disappointing results of topical phenylephrine in the treatment of faecal incontinence. They concluded that this treatment did not produce a significant improvement in symptoms or function. However, six patients did report a greater than 75% subjective improvement in symptoms on the active treatment, as did two patients on placebo. The lack of effect of phenylephrine in the patients studied is attributed to the dosage used and the authors hypothesize that the lack of response may also be related to the severity of sphincter degeneration, i.e. unresponsiveness to extrinsic stimulation caused by fibrosis and/or atrophy. Indeed, this may be very true because it has been reported that there is a relationship between the patient's age and the endosonographic thickness of the internal anal sphincter[1]. The six patients had a short duration of symptoms, suggesting that these were young patients. In this respect it would be very useful to know whether there was a relationship between either age or duration of symptoms and the effect of treatment as we recently demonstrated that there was no correlation between age and atrophy of the *external* anal sphincter as seen on endoanal magnetic resonance imaging[2]. This is in accordance with the results published by Shafer *et al.*[1] who found that age-related changes of function were only found for resting pressures, i.e. the internal anal sphincter. Until this issue has been clarified, the authors' conclusions may require some qualification.

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1 Schafer R, Heyer T, Gantke B, Schafer A, Frieling T, Haussinger D *et al.* Anal endosonography and manometry: comparison in patients with defecation problems. *Dis Colon Rectum* 1997; **40:** 293–7.
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Authors' reply

Sir

We thank Dr Briel and colleagues for their interest in our paper. Our study was the first attempt at treating the difficult problem of passive faecal incontinence in a group of patients without a structural sphincter injury. Most patients had a slightly decreased voluntary sphincter contraction suggesting minimal external sphincter dysfunction, but the main problem was a weak internal sphincter causing passive incontinence. External anal sphincter atrophy was therefore unlikely to account for the negative results of the study. Despite the well documented relationship between age, endosonographic thickness of the internal sphincter, and function of the internal sphincter, we found no relationship between age and effectiveness of treatment. However, patients who responded did have a significantly shorter duration of symptoms compared with nonresponders, although the numbers were too small for meaningful statistical comparison. Not all responders showed elevation of the resting sphincter pressure with treatment and effective treatment of faecal incontinence is likely to be more complicated than just raising the sphincter pressure. We are currently undertaking studies using higher doses of phenylephrine. These have shown a more profound effect on the sphincter and further results will be presented in due course.

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Mortality from ruptured abdominal aortic aneurysm in Wales

Sir

We read with interest the study by Basnyat *et al.* (*Br J Surg* 1999; **86:** 765–770). Data was collected from 18 Hospitals and it would have been interesting to know how each unit compared in terms of operative survival and proportion of patients rejected for operation. Some Hospitals might be better prepared for such emergencies, for example, a reduced 'door to theatre time', more efficient haematology services and better access to an emergency theatre. Did a successful outcome and/or a positive selection for operation depend on the Hospital of presentation rather than the speciality of the receiving consultant? Consultants without an interest in vascular surgery rejected more patients for operation than those with, but the criteria used for selection or rejection and the condition of the patients at presentation is not mentioned. The difference in rejection rates may therefore be because:

1. The selection criteria was the same but POSM scores of patients on arrival were higher with the general surgeons.
2. The POSM scores were the same but the vascular surgeon had a lower threshold for operation.

With these unaddressed variables is it possible to compare the outcomes between the two specialties?

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Authors' reply

Sir

We thank Messers Logan and Bourantas for their interest in our article. In our study, data were collected prospectively from 18 Hospital in Wales. The purpose of the study was to identify the incidence of rupture AAA and mortality from rupture AAA in patients reaching Hospital alive. Data on 'door to theatre time', efficiency of haematological service (which we doubt will alter the management of ruptured AAA) and availability of emergency theatre in the Hospital or at the time of presentation were not collected. The number of patients with ruptured AAA reaching Hospital alive ranged from 2 to 24 patients (median 13). The number in each Hospital was too small to compare statistically.

The outcome of surgeons with vascular interest compared with general surgeons probably represents a national situation as vascular surgical cover is not always available. Certainly we understand there is a similar finding in a recent Scottish audit (personal communication). We do, however, accept the fact that there are many variables. No criteria for either intervention nor nonintervention were specified and this was the decision of each individual consultant responsible for that particular patient. As the number of patients per consultant were small, comparisions between them were not possible.

The most important message from our study is that mortality from ruptured AAA is excessively high even in the hands of the most experienced vascular surgeon.

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Fatal and life-threatening complications in antireflux surgery: analysis of 5502 operations

Sir

We congratulate Rantanen *et al.* (*Br J Surg* 1999; **86:** 1573–77) for their large retrospective study of patients who have undergone antireflux surgery. They conclude that more life threatening complications occur in the laparoscopic group with fewer advantages to it. This does seem contrary to the results derived from randomized and nonrandomized trials of open *versus* laparoscopic fundoplication[1,2]. In fact some reports indicate that the complication rate is higher for open rather than laparoscopic surgery[3]. In the discussion they note that the majority of the complications occurred in 1993, a year after the adoption of the laparoscopic approach. It would have been interesting to examine the incidence of complications in time periods with relation to the learning curve for this procedure. It is now accepted that laparoscopic surgery has a learning curve and this has been described in laparoscopic fundoplication[4,5]. The mean operative time, Hospital stays and conversion and complication rates diminish with experience in the procedure.

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3 Viljakka MT, Luostarinen ME, Isolauri JO. Complications of open and laparoscopic surgery: 32-year audit at a teaching hospital. *J Am Coll Surg* 1997; **185:** 446–50.
4 Deschamps C, Alien MS, Trastek VF, Johnson JO, Pairolero PC. Early experience and learning curve associated with laparoscopic fundoplication. *J Thorac Cardiovasc Surg* 1998; **115:** 281–4.
5 Coelho JC, Wiederkehr JC, Campos AC, Andrigueto PC. Conversions and complications of laparoscopic treatment of gastroesophageal reflux disease. *J Am Coll Surg* 1999; **189:** 356–61.

Authors' reply

We thank Doctors Darzi and Moorthy for their valuable commentary on our study[1]. We agree that the overall minor complications including incisional hernias may be less frequent after laparoscopic technique[2] but there are few studies dealing with serious complications after antireflux surgery involving adequate numbers of patients, laparoscopic fundoplication, and covering a range of Hospitals. Our study demonstrated more serious complications after laparoscopic than open techniques. Perforation was the commonest serious and life-threatening complication of laparoscopic fundoplication and our finding is contrary to those presented by Darzi and Moorthy[3–5]. There were many short-comings in these studies including small numbers of patients and historical comparisons[3,4] and in the study of Laine et al.[5] the open procedures were performed by surgical residents and laparoscopic operations by experienced laparoscopic surgeons. Far reaching conclusions cannot therefore be drawn from these studies. The incidence of serious complications after laparoscopic technique in different time periods and in the learning curve cannot be answered because of our study design. According to meta-analysis of studies published recently and involving both open (1984–97; 1563 patients, 12 perforations) and laparoscopic fundoplication (1993–97; 905 patients, 18 perforations) the prevalence of perforations was significantly higher in laparoscopic fundoplication. In addition to serious complications functional outcome has been found to be worse after laparoscopic fundoplication[2–6]. The only multicentre randomised trial had to be stopped because of the high incidence of severe dysphagia after laparoscopic fundoplication. The advantages of laparoscopic antireflux surgery may not be as good as supposed.

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2 Frantzides CT, Carlson MA. Laparoscopic versus conventional fundoplication. *J Laparoendosc Surg* 1995; **5:** 137–43.
3 Viljakka MT, Luostarinen ME, Isolauri JO. Complications of open and laparoscopic surgery: 32-year audit at a teaching hospital. *J Am Coll Surg* 1997; **185:** 446–50.
4 Deschamps C, Allen MS, Trastek VF, Johnson JO, Pairolero PC. Early experience and learning curve associated with laparoscopic fundoplication. *J Thorac Cardiovasc Surg* 1998; **115:** 281–4.
5 Coelho JC, Wiederkehr JC, Campos AC, Andrigueto PC. Conversions and complications of laparoscopic treatment of gastroesophageal reflux disease. *J Am Coll Surg* 1999; **189:** 356.61.
6 Bais JE, Bartelsman JF, Bonjer HJ, Cuesta MA, Go PM, Klinkenberg-Knol EC *et al.* (The Netherlands Antireflux Surgery Study Group) Laparoscopic or conventional Nissen fundoplication for gastro-oesophageal reflux disease; randomised clinical trial. *Lancet* 2000; **355:** 170–4.

Cost-effective carotid endarterectomy

Sir

I read with interest the article by Sandison *et al.* (*Br J Surg* 2000; **87:** 323–327) and feel that the term 'cost-effective' is used inappropriately. Cost effectiveness is a form of full economic evaluation defined as a comparative analysis of alternative courses of action, in terms of their cost and consequences[1]. The consequences are usually unidimensional clinical outcome measures such as cost per life saved, cost per stroke avoided, etc. The authors have not measured any such outcome. It appears from the study that the outcomes were similar even though all patients were not extensively investigated, were admitted to the intensive care unit following surgery or stayed longer in the Hospital. In terms of economic evaluation this may be considered a cost minimization analysis. This is a special form of cost-effectiveness analysis where the consequences of the alternative treatments being compared turn out to be equivalent[2]. None of the principles of a full economic evaluation seem to have been followed and it is difficult to comment on which form of evaluation it could have been. The statement that the estimated median cost saved per carotid endarterectomy per year was calculated by adding the cost saved on investigations and intensive care for an average patient per year to the median length of stay for that year is confusing.

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1 Jonsson B. Cost-effectiveness: a new criterion for selecting therapy. *J Int Med* 1995; **237:** 1–3.
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Author's reply

I thank Mr Kumar for his interest in our paper. I agree that the term 'cost-effectiveness' has not been used in the strict sense as defined by health economists. This would require the cost of carotid endarterectomy to be divided by the number of stroke-free life years gained. This is usually performed in the context of clinical trials which follow up patients for a number of years. Unfortunately, we could not gather accurate figures for some of the costs involved in carotid endarterectomy, particularly the cost of theatre usage. However, because of the directorate system at Guy's most of the costs involving other Departments were easily identifiable. I feel sure that the majority of surgeons reading the article would understand that reducing investigations, the use of intensive care and Hospital stay would result in a reduction in the cost of carotid endarterectomy. Our main point was that the postoperative morbidity and mortality was not affected by these reductions.

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Specialized intestinal metaplasia in patients with gastro-oesophageal reflux disease

Sir

Carton *et al.* (*Br J Surg* 2000; **87:**116–21) conclude that specialized intestinal metaplasia (SIM) at the gastro-oesophageal junction is not associated with *H. pylori* infection. Unfortunately their methodology may not be adequate to support this conclusion. The authors are very likely to have seriously underestimated the prevalence of current and past *H. pylori* infection in their cohort. The authors used 4 cardiac and one antral biopsy, processed by 'standard histological techniques', to detect *H. pylori.* To accurately detect *H. pylori*, at least 2 gastric corpus and 2 antral biopsies are recommended to give sufficient sampling, as the infection can be scanty and focal[1]. Because *H. pylori* colonizes gastric epithelium, when intestinal metaplasia is present, bacterial density is much reduced and greater biopsy sampling is required[2]. Similar deficiencies are seen in the other studies quoted which failed to demonstrate such an association.

In contrast, there are 3 studies with superior methodology (multiple distal stomach biopsies combined with Giemsa staining and serology), which show a significant association between *H. pylori* and SIM[3–5]. El-Serag *et al.* found no patients with carditis not associated with *H. pylori* infection in 302 subjects. They described 50 patients with SIM at the cardia and this was strongly associated with *H. pylori* but with Gastro-oesophageal reflux disease[5]. Goldblum *et al.* also failed to find any association between reflux and carditis. In fact SIM at the cardia was less common in those with GORD. Only one of 34 patients with carditis had no evidence of *H. pylori* infection and 7/8 with cardiac SIM had *H. pylori* infection[4].

Further studies investigating the relationship between *H. pylori*, SIM and reflux may clarify the issue but it is essential that they utilize adequate methodology.

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1 Technical annex: Tests used to assess Helicobacter pylori infection. Working Party of the European Helicobacter pylori Study Group. *Gut* 1997; **41** (Suppl. 2): S10–23.
2 Beales I, Crabtree JE, Scunes D, Covacci A, Calam J. Antibodies to CagA protein are associated with gastric atrophy in Helicobacter pylori infection. *Eur J Gastroenterol Hepatol* 1996; **8:** 645–9.
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Management of the axilla in operable breast cancer treated by breast conservation: a randomized clinical trial

Sir

I was interested in the article the Management of the axilla in operable breast cancer by Chetty *et al.* (*Br J Surg* 2000; **87:** 163–9) which essentially described the 'Edinburgh thesis on axillary management', i.e. that axillary lymph node sample adequately reflects nodal pathology and allows radiotherapy when nodes are positive.

I am a little surprised at the axillary recurrence rates in the two groups (8 of 232 clearances and 7 of 234 samples, and if supraclavicular recurrences are included, the figures are, respectively, 12 and 10) over a relatively short period of follow-up. One has to be concerned about the adequacy of the clearance technique, a suspicion further confirmed by the, admittedly gratifyingly, low incidence of arm oedema in the clearance group.

Hopefully the management of the axilla is now evolving with the investigation of the prognostic significance of the sentinel node as an indicator of metastatic axillary disease. If sentinel node biopsy can be proved reliable, some 65% of women with symptomatic disease and 80% of women with screen-detected carcinoma would not need to undergo any further axillary procedure. This, in itself, should produce a very significant reduction in the incidence of lymphoedema[1] without jeopardising local recurrence.

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1 Wedgwood KR, Benson EA. Morbidity and mortality after modified radical mastectomy. *Br J Cancer* 1990; (Suppl. XII), 13.

Letter 2

Sir

This randomized clinical trial by Chetty *et al.* comparing axillary node clearance and axillary node sample with or without radiotherapy to the axilla is highly commendable[1] but there are some confounding factors which ought to be borne in mind when interpreting the findings.

In all, 42 patients who were *node negative* underwent axillary radiotherapy and 5 patients who were *node positive* did not undergo axillary radiotherapy. There were a total of 87 protocol violations (18.6%). These deviations may skew the results.

It would have been helpful to have performed quality of life studies because the significant finding relating to surgical morbidity occurred in the group who underwent radiotherapy where lateral and medial rotation were reduced at 6 months and deteriorated with time. Was this morbidity greater or less than the morbidity related to a 4.1% increase in 'lymphoedema' as measured of this objectively by arm circumference. A subjective assessment by the patients of this morbidity would have been helpful and allowed clearer conclusions.

Finally, it would be useful if the authors could provide selection criteria for patients at *intermediate* risk of axillary node involvement.

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1 Chetty U, Jack W, Prescott RJ, Tyler C, Rodger A. Management of the axilla in operable breast cancer treated by breast conservation: a randomized clinical trial. *Br J Surg* 2000; **87:** 163–92.

Author's reply

Sir

I thank Messrs. Benson and Purushotham for their interest in our paper.

The type of axillary surgery performed in the Study was a full level 3 clearance with division of pectoralis minor. The axillary recurrence rate in those patients randomized for a clearance was in the region of 3% at a median follow up of 4 years. Studies[1,2] showing a lower axillary recurrence rate only included patients with a clinically negative axilla (N0). This may account for the differences.

I agree with Mr Purushotham that protocol violations are a potential problem in studies but the analysis of local recurrence and survival was done strictly on an intention to treat basis, as two surgical approaches to the axilla were being examined. The assessment of morbidity was done using objective measurements to provide hard data to analyse.

However, I do agree that some form of subjective assessment of symptoms and quality of life would have augmented this study.

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1 Fisher B, Redmond C, Fisher ER, Bauer M, Wolmark N, Wickherham DL *et al.* Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. *N Engl J Med* 1985; **312:** 674–81.
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Randomized clinical trial of haemorrhoidectomy under a mixture of local anaesthesia *versus* general anaesthesia

Sir

I congratulate Ho *et al.* (*Br J Surg* 2000. **87:** 410–413) on their randomized clinical trial of haemorrhoidectomy under a mixture of local anaesthesia (LA) *versus* general anaesthesia (GA). This clinical data will be of value for those treating prolapsing haemorrhoids particularly in the present climate of bed pressures resulting in an increasing emphasis on day case treatment[1]. There are, however, some issues which merit comment.

The innovative technique used for keeping the EMLA cream in contact with the anoderm (using an occlusive guaze dressing impregnated with paraffin) obviously works well. However, with 10 g (2 tubes) of the application being applied at the stated concentration (lignocaine 25 mg and prilocaine 25 mg per gram), it is feasible that a considerable amount may be directly absorbed from the anoderm into the systemic circulation. Combined with infiltration with up to 15 mL 0.5% bupivacaine at operation dangerously high levels of circulating local anaesthetic may result. The authors conclude that LA haemorrhoidectomy should be recommended for patients with cardiorespiratory comorbidity; a group of patients particularly susceptible to LA toxicity.

A significant percentage (63%) of the LA patients requested sedation with midazolam (dose not stated) intraoperatively. With the retrograde amnesic properties of midazolam, could patients reliably remember the procedure in order to grade the intraoperative pain experienced?

Finally, the use of topical LA is unlikely to be of benefit to patients undergoing stapled haemorrhoidectomy, where the mucosal resection and anastomosis is carried out well above the dentate line in a region of fewer pain sensitive receptors.

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1 Carapeti EA, Kamm MA, McDonald PJ, Chadwick SJD, Phillips RKS. Randomized trial of open versus closed day-case haemorrhoidectomy. *Br J Surg* 1999; **86:** 612–3.

Authors' reply

Sir

We thank Dr Beattie for the interest in our article. EMLA cream is applied over the intact anoderm before surgery and is then wiped off when the patient is cleaned before surgery commences. EMLA is a very safe drug, which gives systemic blood levels of between 1/20 and 1/50 of the toxic level[1]. Even in combination with 15 mL of 0.5% bupivacaine this is well below a toxic dose. There were no reports of drug toxicity in our study and we recommend the use of EMLA even in patients with cardiorespiratory comorbidity.

None of the patients had retrograde amnesia and all could grade the intraoperative pain experience.

We have not tried the use of topical LA in patients undergoing stapled haemorrhoidectomy but agree that there are few pain receptors above the dentate line. We believe that some form of anaesthesia should be given in this procedure as it would facilitate the application of the purse-string suture and the insertion of a size 33 stapling device.

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1 White PF. *Anesthesia Drug Manual.* Philadelphia: W.B. Saunders Company, 1996: Pp 184.

Book reviews

The Role of Surgery in AIDS – An Outcomes Based Approach

D. R. Flum, M. K. Wallack (eds)

254 x 177mm. Pp. 358. Ilustrated. 1999. Philadelphia, Pennsylvania: Lippincott, Williams & Wilkins. $59.95.

This book contains facts, figures and opinions relevant to surgery in patients with HIV and AIDS. A lot of information is necessarily anecdotal and little is derived from clinical trials. The authors have extensive experience of surgery in HIV infected patients and they, if anyone, can (and do) provide a considered opinion of the present situation. The experience is USA based and the views expressed reflect this. Much thought has gone into most of the 18 chapters but style and structure vary considerably. Outcome related information is identified by l in the margin; nine chapters have more than two such sections. There are good chapters on anaesthesia and critical care, emergency and abdominal, cardiac, colorectal, hepatobiliary and orthopedic surgery. It is a reflection on the nature of AIDS that it is now possible to write 22 pages (with 231 references) on splenic surgery. That AIDS demands a rethinking of surgical priorities is illustrated by the assertion that: 'a potentially adverse effect of the use of tubal sterilization is decreased condom use' (gynecological surgery). Surprisingly there is not a chapter on urological surgery and there is a paucity of information on how to treat 'ordinary' surgical disease in patients who happen to have HIV/AIDS. This is a timely book documenting the development of surgery in a new era. It demonstrates how experienced observation can effectively advance surgical knowledge and thought.

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Textbook of Erectile Dysfunction

C. Carson, R. Kirby, I. Goldstein (eds)

282 × 226 mm. Pp. 659. Illustrated. 1999. Oxford, UK: Isis Medical Media. £120.00.

This textbook provides a comprehensive review of the major aspects of erectile dysfunction, with contributions from many of the acknowledged experts in this field. The book is aimed at the clinician with a major interest in erectile dysfunction and provides up-to-date information concerning the management of this condition. Following a detailed review of penile anatomy and physiology, the pathophysiology is covered in a number of chapters, along with a detailed review of the current investigations available to the clinician. The wide variety of treatment options now available for erectile dysfunction are discussed, including the current status of surgical management. Each treatment is critically examined and this, by clearly documenting the various success rates and complications, provides the physician with valuable information for use in clinical practice. The volume, which is presented in a clear, concise and extremely readable fashion, will be of particular interest to surgeons, physicians and health care workers interested in erectile dysfunction. It provides an important reference text for individuals undertaking research in this field.

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The Washington Manual of Surgery – 2nd Edition

G. M. Doherty, J. B. Meko, J. A. Olson, G. R. Peplinski, N. K. Worrall (eds)

215 × 150 mm. Pp. 698. Illustrated. 1999. Philadelphia, Pennsylvania: Lippincott, Williams & Wilkins. $ 37.95.

This volume is written by the resident staff of Washington University, St Louis, each of whom is assisted by a senior coauthor. The first 10 chapters (comprising 25% of the text) cover aspects of pre-, peri-, and postoperative care, all of which are written understandably with a North American perspective. The indicative blood results and the normal serum ranges given in a later appendix suffer from the same problem and are not in Systeme International (SI) units. There follows a series of chapters presented on a systematic basis, with brief but thorough presentations of diagnosis, treatment and outcome. A final chapter 'Common Surgical Procedures' provides useful information on the insertion of lines and drains. The manual is designed to be pocket sized and is aimed at surgical trainees, but how useful is it in a non-American setting? It is packed with information in a spiral binder between cardboard covers. As a textbook to learn from, it lacks photographs and diagrams, and the text is densely packed and small, making it difficult to read. At 700 pages and weighing 600 g, it does not easily fit in the pocket, and the review copy is already showing signs of wear. These defects, combined with the North American slant, will limit its value to the British trainee.

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Handbook of Trauma: Pitfalls and Pearls

R. F. Wilson (ed.)

216 × 133 mm. Pp. 795. Illustrated. 1999. Philadelphia, Pennsylvania: Lippincott, Williams & Wilkins. $42.95

This handbook is a condensed edition of a more comprehensive (probably multiauthored) treatize on trauma. The spectrum of the contents spans over the whole breadth of trauma surgery, with each one of the 40 odd chapters dealing with a specific organ, system, anatomical region, patient group or topic. The conventional lay-out of these sections is interrupted here and there by boxed statements titled 'axioms' which purport to emphasize a point of management. The chapters end with a list of pitfalls, termed 'frequent errors' followed by 'summary points', a list of numbered statements offering the reader a few (perhaps too many) pearls of wisdom. I found the coverage of the subject matter of an extremely high standard. For a handbook, there is, surprisingly, a wealth of information even for the seasoned trauma surgeon, and the authors do not shy away from taking a stand (and usually a reasonable and pragmatic one) on the usual management controversies. The intended readership is not the senior trauma fraternity and the primordial objective of the text is to drum home a message; this has been achieved at the price of a tedious repetitiveness of the important points on each topic. However this is a minor criticism and, on occasions when pressed by time, I found myself skipping the main body of the text and scanning instead the 'axioms'; 'frequent errors' and 'summary points'. Another relatively minor criticism is the choice of the references which are sometimes dated or parochial. All in all, 1 believe that this is the best short text on trauma I have come across recently.

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Manual of trauma and emergency surgery

D. V. Shatz, O. C. Kirton, M. G. McKenny J. M. Civetta (eds)
227 × 150 mm. Pp. 319. Illustrated. 1999. Philadelphia, Pennsylvania: W. B. Saunders.

Trauma accounts for more years of life lost in the USA than cancer and heart disease combined. The resultant costs of long-term disability are astronomical. To achieve the best possible outcome, the severely injured patient requires accurate assessment and appropriate intervention from the start. This little gem of a book is designed to provide the reader with a rapid reference and an algorithmic approach to the initial therapy of specific injuries. The 24 chapters, written by 20 collaborating authors, provide a synopsis of basic surgical principles in acute trauma and emergency surgery management. Information is presented in a concise, clear and easy to read style, and the reader will find that most of the essentials of trauma and emergency surgery are well covered. The algorithms are clearly set out and each algorithm has a useful explanatory key. The accompanying text is succinct and logically presented. The references listed at the end of each chapter are up to date and comprehensive.

The book covers most of the important areas in trauma, including triage, scoring systems, disaster management, emergency airway management and techniques for airway control, including specific clinical situations such as cervical spine injury, tracheal and head injury, and facial burns and airway injury. Further chapters cover head injuries, penetrating neck, chest and praecordial injuries, blunt thoracic trauma, rib fractures and hypoxia, acute spinal cord injury, abdominal trauma, genitourinary trauma, crush, and pelvic and extremity injuries. I was delighted to find a chapter devoted to organ injury scoring systems. The section on emergency surgery provides a comprehensive approach to the acute abdomen, acute gastrointestinal haemorrhage, intestinal obstruction and abdominal vascular emergencies. Finally, tucked at the back, is a chapter which provides a step by step 'how to do it' section on the common procedures and techniques used for resuscitation. These include cricothyroidotomy, tracheostomy, tube thoracostomy, subclavian line placement, saphenous vein cutdown and pericardiocentesis. The line drawings accompanying the text are excellent, The book slips easily into a coat pocket and is a must for trainees dealing with trauma and surgical emergencies.

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Vascular Surgery – 5th edition

R. B Rutherford (ed.)
285 × 222 mm. Pp. 2266. Illustrated. 1999. Philadelphia, Pennsylvania: W. B. Saunders. £199.00.

This very American textbook has come to be recognized internationally as the 'bible' of vascular surgery. Nowadays it is published as two volumes, the physical weight of the work perhaps reflecting the authority of the 'heavyweight' multiauthorship. With such a distinguished history, a general overview of the contents (which are truly extensive) is perhaps unnecessary. More to the point is whether or not the present offering has built adequately on its antecedents. Is it up to date? Does it reflect the significant changes that have occurred in vascular surgery since the publication of its previous (4th) edition? Well, the number of chapters has increased by 13–166, but some of the older chapters have been merged such that the total number of topically new chapters is actually 20. In addition, most of the older chapters have been extensively revised and many new authors have contributed to this undoubtedly up to date publication. This reviewer was unable to find any area of vascular surgery that is not covered; in particular, endovascular procedures and modern imaging techniques have been allotted the space they deserve. If there is any weakness in the book it can only be that some of the black and white illustrations are a little dull and unappealing; all colour reproduction has been placed at the front of the volume as 'plates' and while this cuts costs it is a rather awkward feature. At 2266 pages (excluding the index, contents section, colour plates, etc.) 'Rutherford' is hardly a book that many will read from beginning to end, but it is the best reference work in vascular surgery yet available. Among vascular textbooks it will remain pre-eminent as a source for clinical enquiry, lecture generation and medicolegal guidance over the next few years. Its competition in the future, one suspects, will not come from other ink on paper products but from electronic reference works.

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Endoscopic Gastric Surgery

E. Hanisch, M. Kitajima, T. Wehrmann, A. Encke (eds)
240 × 160 mm. Pp. 134. Illustrated. 2000. Berlin: Springer. £57. 50

This book initially appears attractive. It is short (nine chapters, 132 pages) and published by a well established medical publisher with a typeface that is easy to read. On initial thumbing through it appears to have some good quality line drawings and laparoscopic photographs. The subjects encompassed are reflux disease, achalasia, morbid obesity, gastric mucosal resection and gastrectomy. Superficially it appears a good buy but, regrettably, I am unable to recommend this book.

The authors are from Germany and Japan. A publishing house as international as Springer should not only be able to find adequate translators but, prior to setting the manuscript to print, should have ensured the text was read by someone whose native language was English. The production lacks consistency: the chapters on technique of antireflux surgery, achalasia and morbid obesity are preceded by chapters on the physiology and diagnosis of these conditions. This format is not followed for the chapters on laparoscopic gastric resection. Many of the illustrations are superfluous and add little to the text (three photographs of the postlaparoscopy abdominal wall) and some are downright confusing, such as the oesophageal pH and manometry traces. These are of scant value to those whose daily life involves their interpretation and, without legends, they are totally indecipherable to the nonexpert. The physiological chapters contain sound and basic information but lack details of recently published trials of therapy. The chapter on fundoplication technique is not a clear description and details of postoperative complications are somewhat muddled. Deficiencies include lack of any mention of laparoscopic repair of rolling hiatus hernia or of the thoracoscopic approach to cardiomyotomy for achalasia. For a book that is entitled 'Endoscopic Gastric Surgery' there are no texts on laparoscopic staging for gastric or gastro-oesophageal carcinoma. The chapters on gastric resection are interesting from a technical view but are difficult to understand on first reading, largely due to poor English. Some of the colour illustrations add little and could be replaced by good line drawings. This book is neither a textbook on operative technique nor an authoritive text on the pathophysiology of upper gastrointestinal disorders; as such, it does not fit readily into the reading list of either trainee or established surgeon. It appears to have been edited and produced in a hurry, with inadequate thought as to content, readership or production.

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General Thoracic Surgery. 5th Edition

T. W. Shields, J. LoCicero III, R. B. Ponn (eds)
285 × 223 mm. Pp. 2443. Illustrated. 1999. Philadelphia, Pennsylvania: Lippincott, Williams & Wilkins. $259.

This, the latest edition of the Shields textbook, is appreciably larger than the last. The senior author has recruited the assistance of two associate editors, Dr LoCicero and Dr Ponn. The two-volume format has been retained, but expanded by almost a third, and there are now 2443 pages and 190 chapters. Expansion has mostly occurred in the sections on 'The Mediastinum', which now has 43 chapters. Most of this additional material has been drawn from the senior author's textbook on 'Mediastinal Surgery". There are several new chapters that cover the expanding role of video-assisted thoracoscopic surgery, developments in basic science and new surgical techniques. A new chapter on statistical analysis is most welcome, although consigned to the appendix. Most of the chapters retained from the previous edition have been updated and revised. There has been some reshuffling of the contents, most of these changes being logical. The second volume now contains only those sections on the oesophagus and the mediastinum, leaving it considerably smaller than volume one. The changes and additions to the fifth edition ensure that this standard textbook remains contemporary and comprehensive.

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Scientific Surgery

Hasegawa H, Radley S, Morton DG, Keighley MR. Stapled versus sutured closure of loop ileostomy: a randomised controlled trial. *Ann Surg* 2000; **231:** 202–4.

Hosital stay, reoperation and readmission rates were similar in the 141 operations studied. The rate of postoperative bowel obstruction was lower after stapled ileostomy (2/71 *versus* 10/70).

Julien J-P, Bijker N, Fentiman IS, Peterse JL, Delledonne V, Rouanet P *et al.* Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomized phase III trial 10853. *Lancet* 2000; **355:** 528–33.

Over 1000 patients were randomized after complete excision of DCIS to radiotherapy or no treatment. A mean of 4 years radiotherapy improved the relapse-free rate from 84 to 91 per cent ($P = 0.005$).

Dutch Bypass Oral anticoagulants or Aspirin (BOA) Study Group. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery: a randomized trial. *Lancet* 2000; **355:** 346–51.

Some 2690 patients were included. Oral anticoagulation reduced the rate of vein graft occlusion (hazard ratio 0.69). Aspirin was better for patients with a prosthetic graft and had fewer bleeding complications.

Grief R, Akca O, Horn E-P, Kurz A, Sessler DI. for the Outcomes Research Group. Supplemental perioperative oxygen to reduce the incidence of surgical wound infection. *N Engl J Med* 2000; **342:** 161–7.

Five hundred patients were randomized to receive either 30 or 80% oxygen during, and for 2 h after elective colorectal surgery. The supplemental oxygen reduced the rate of wound infection from 26 to 13 per cent ($P = 0.01$).

Hollington P, Toogood GJ, Padbury RTA. A prospective randomized trial of day-stay only versus overnight-stay laparoscopic cholecystectomy. *Aust NZ J Surg* 1999; **69:** 841–3.

Some 131 patients were included; 18 per cent of day cases needed overnight admission and 18 per cent of overnight patients stayed more than one night. Two and three patients in each group, respectively, required readmission. Hospital costs were similar.

Zdanowski Z, Danielsson G, Jonung T, Norgren L, Ribbe E, Thorne J *et al.* Intraoperative contamination of synthetic vascular grafts. Effect of glove change before graft implantation. A prospective randomised study. *Eur J Vasc Endovasc Surg* 2000; **19:** 283–7.

Changing surgical gloves had no effect on the rather high rate of isolation of bacteria from gloves and bypass grafts in this investigation including 40 patients.

Bozetti F, Gavazzi C, Miceli R, Rossi N, Mariani L, Cozzaglio L. Perioperative total parenteral nutrition in malnourished, gastrointestinal cancer patients: a randomised clinical trial. *J Ent Parent Nutr* 2000; **24:** 7–14.

Ninety patients with gastric or colorectal tumours and weight loss of more than 10 per cent were studied. TPN reduced the postoperative complication rate from 57 to 37 per cent ($P = 0.03$), and the mortality rate from five to nil ($P = 0.05$).

Friemert B, Faoual J, Holldobler G, Becker HP, Lampl L, Gerngross H. A randomized controlled study for inguinal hernia repair according to the Shouldice technique. *Chirurgie* 2000; **71:** 52–7.

Patients randomized to local anaesthesia suffered significantly less pain for up to 3 days after surgery than those who had general anaesthesia in this study including 60 patients.

Fevang BT, Jensen D, Fevang J, Sondenaa K, Overbo K, Rokke O *et al.* Upper gastrointestinal contrast study in the management of small bowel obstruction: a prospective randomised study. *Eur J Surg* 2000; **166:** 39–43.

Some 98 patients with small bowel obstruction on plain X-ray were enrolled. Gastrograffin meal did not contribute significantly to management as outcomes were similar, but time to surgery after contrast examination was shorter.

Arbman G, Krook H, Happaniemi S. Closed versus open haemorrhoidectomy — is there any difference? *Dis Colon Rectum* 2000; **43:** 31–4.

This was a study of 77 patients with second degree haemorrhoids. Both methods were effective and there were no differences in pain, complications or Hospital stay. Significantly more patients were healed completely 3 weeks after closed haemorrhoidectomy (86 *versus* 18 per cent).

Ho Y-H, Tan M, Seow-Choen F. Micronized purified flavonidic fraction compared favorably with rubber band ligation and fiber alone in the management of bleeding hemorrhoids: a randomized controlled trial. *Dis Colon Rectum* 2000; **43:** 66–9.

Some 162 patients with bleeding, nonprolapsed haemorrhoids were randomized into three groups. Fastest relief of bleeding was with flavonidic fraction plus high fibre diet; there were no differences in the rates of late recurrence.

Girolami B, Bernardi E, Prins MH, ten Cate JW, Prandoni P, Simioni P *et al.* Antiplatelet therapy and other interventions after revascularisation procedures in patients with peripheral arterial disease: a meta-analysis. *Eur J Vasc Endovasc Surg* 2000; **19:** 370–80.

This paper analysed 32 studies. Aspirin with dipyridamole improved graft patency and mortality, ticlopidine improved graft patency and reduced the amputation rate, but studies with warfarin were inconclusive.

Bulmer M, Hartley J, Lee PWR, Duthie GS, Monson JTR. Improving the view in the rectal clinic: a randomised control trial. *Ann R Coll Surg Engl* 2000; **82:** 210–2.14.

The trial evaluated the effect of a self-administered glycerine suppository before outpatient rigid sigmoidoscopy in 131 patients. Compliance was high and the suppository increased the number of successful examinations.

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The *British Journal of Surgery* subscribes to the policy of uniform requirements for manuscripts which facilitates resubmission of papers to journals without extensive recasting. Authors are advised to consult the *New England Journal of Medicine* (*N Engl J Med* 1997; **336**: 309–15), or obtain 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £2·95 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. **When quoting specific materials, equipment and proprietary drugs you must state in parentheses the brief name and address of the manufacturer.** Generic names should normally be used.

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The Editorial Board of the *British Journal of Surgery* encourages submission of review articles or meta-analyses on topics of interest. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted article will receive an honorarium. Before submission of a meta-analysis of randomized trials, authors are encouraged to consult the QUORUM statement, designed to assist in improving the quality of the submission (*Lancet* 1999; **354**: 1896–900). Potential authors are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

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The Editors commission leading articles that are 600–900 words in length and address controversial topics of current interest. They should be supported by no more than ten key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

Correspondence

The Editors welcome topical correspondence. Letters should not exceed 250 words and should be typed double-spaced.

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On the title page give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) **the name, postal and email addresses, telephone and facsimile numbers of the author responsible for correspondence and to whom requests for reprints should be addressed;** (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, review, etc).

Abstract

This must not exceed 200 words and should be presented in a structured format. **Background**: state why the study was done and its main aim. **Method**: describe patients, laboratory material and other methods used. Clearly identify the nature of the study, i.e. randomized controlled trial, retrospective review, experimental study, etc. **Results**: state the main findings including important numerical values. **Conclusion**: state the main conclusions but controversial or unexpected observations may be highlighted.

Tables and illustrations

Submit four copies of all illustrations and tables. Type each table on a separate page with a brief title. Line drawings are acceptable as clear black on white graphics, computer print-out or photocopies. Submit radiographs, photomicrographs, etc unmounted in the form of glossy prints, original transparencies or negatives. Illustrations in colour are encouraged and will be printed at no cost to the author. If you include photocopies, they should be of sufficient quality to enable the Journal's referees to judge their content and value. Label each illustration on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); indicate the top of the illustration. Include a measure of magnification of photomicrographs. Include explanations of symbols and shading within the figure. Survival curves must be accompanied by a table giving the actual numbers of patients involved. Include in the legends to illustrations and the footnotes to tables brief but comprehensive explanations of all the information presented. Look at recent issues of the Journal for examples of accepted layout. Any table or illustration reproduced from a published work must give the original source in full. You must obtain permission from the original author and the publisher before submission.

Abbreviations

Use abbreviations *sparingly*. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension. Abbreviations must be used consistently and must be defined on first use.

Numbers and units

Use the decimal point, not a comma, for example 5·7. Use a space and not a comma after thousands and multiples thereof, for example 10 000. Use SI units (International System of Units) except for the measurement of blood pressure (mmHg).

Statistics

For detailed guidance on the handling of statistical material consult *Br J Surg* 1991; **78**: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, the chosen end-points and justify the sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (*JAMA* 1996; **276**: 637–9).

Presentation

Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished and presented in parentheses after the mean values.

Analysis

Clearly describe methods used for each analysis. Methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value. Actual *P* values should be reported to two decimal places, especially when the result is not significant. The results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Take great care in your interpretations. Do not place undue emphasis on secondary analyses.

References

Type the references with double spacing in the Vancouver style (see **Preparation of manuscripts**). Reference to abstracts and personal communications is discouraged. Reference to unpublished communications will not be accepted.

In the text, number references consecutively by superscript:[1] or [1–3]. References cited only in tables or figures should be numbered in sequence.

Leading article

Litigation and surgical practice in the UK

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Few days seem to pass without some reference to allegations of clinical negligence appearing in the press or reported by the media; public demand for high-quality, effective clinical care has never been greater. The cost associated with clinical negligence in England has also come to attention, following a report by the Select Committee on Public Accounts into the *NHS (England) Summarised Accounts 1997–98*[1]. The report reveals that £79 million has already been awarded to patients in 1997–1998 in respect of clinical negligence claims, with projected outstanding liabilities totalling £2·8 billion (£1·8 billion in respect of clinical negligence claims and £1 billion relating to incidents incurred but not yet reported). The true costs, however, could be higher because of recent changes in the way damages are calculated. The extent of those liabilities incurred, but not yet reported, could also be greater than the £1 billion estimate. Such figures place a huge burden on already stretched resources for National Health Service (NHS) patient care. The NHS Executive has calculated that the number of patients seeking compensation in England stands at 15 000; once again, this figure could be higher[1].

To raise the profile of quality of care, the NHS Executive and the UK Government have introduced such concepts as Clinical Governance, National Service Frameworks, the National Institute of Clinical Excellence and improved monitoring of clinical standards. Another important data resource, not yet exploited nationally, would be an analysis of past settled claims. This might provide an insight into the reasons why claims arise and how to prevent them occurring in the future. The Risk Management Department of The Medical Defence Union (MDU) has, for many years, analysed claims to highlight risk trends among specialty groups from a claims database first established in 1977.

The MDU's indemnity and legal costs in 1997 were £67 million, an increase of nearly 20 per cent on 1996 figures, which reflect an inexorable increase in claims and complaints against members. Across all specialties, The MDU has noted a year on year increase of 15 per cent, resulting in a doubling of costs every 5 years owing to a combination of increased frequency and size of claim.

General and vascular surgery claims are, together, the third commonest group of surgical claims settled by The MDU, exceeded only by those for orthopaedic surgery and plastic surgery. They relate largely to routine and frequently performed surgical procedures (*Fig. 1*). In general and vascular surgery, figures for 1999 show a two and a half-fold increase over 1998 and a six-fold increase over 1990 costs. Evidence from hospital practice in the USA has shown that training programmes in risk management techniques for doctors and nurses have resulted in lower rates of claims of negligence[2].

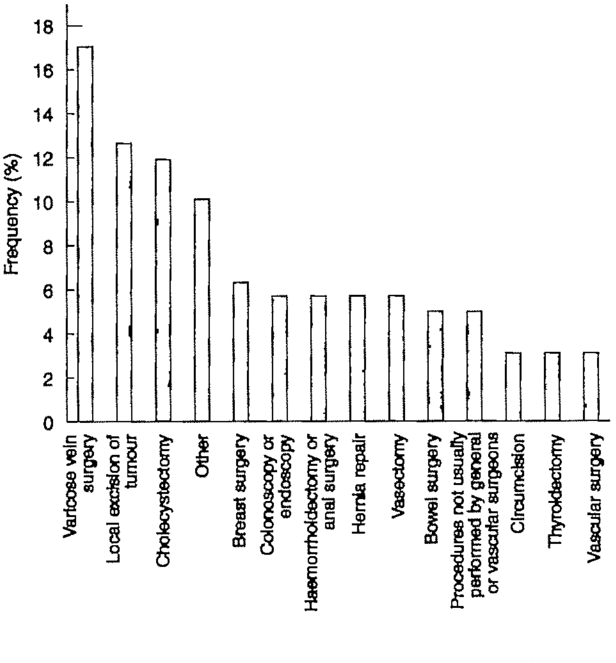

Fig. 1 General and vascular surgery claims settled by The Medical Defence Union in the UK from 1990 to 2000 and related sugical procedures

Claim review

Since the introduction of NHS Indemnity in 1990, The MDU has settled 159 claims involving general and vascular surgeons. The majority arose from private practice and

This is the second in a series of leading articles on litigation and surgery. The experience of continental Europe is examined later in the year.

The MDU 2000

some involved procedures not usually associated with general surgery, for example:

- repair of Dupytren's contracture – resulting in amputation of finger
- breast augmentation – patient dissatisfied with result
- synovectomy of left hallux – damage to common digital nerve
- osteotomy of metatarsal and silastic joint replacement – postoperative infection
- laparoscopic sterilization – perforation of ileum.

All claims in this review were settled because independent expert opinion advised that the standard of care fell below that expected of a reasonable practitioner and that the patient suffered harm as a result.

Indemnity and legal costs were over £8 million. The average time interval from claim to notification was 3 years (range less than 1 to more than 10 years). Settlements ranged from £550 000 following the death of a patient from an undiagnosed deep vein thrombosis (DVT) and pulmonary embolism 4 weeks after elective varicose vein surgery, to £80 for loss of a crown during repeat gastroscopy for gastric ulcer. In the former claim the patient had a previous history of DVT and pulmonary embolism, but no prophylactic anticoagulation was prescribed until the patient exhibited signs of thrombosis 2 weeks after surgery. The second most costly, a vascular claim, resulted in an above-knee amputation following aortobifemoral bypass. No prophylactic antibiotics were prescribed, and antibacterial treatment commenced only when the patient developed an infection in a groin wound. Persistent infection with positive blood cultures resulted, with secondary haemorrhage. Further surgery was required and the amputation was the eventual result. The cost of this claim was over £310 000.

Patients

Of the 159 claims, 51 per cent involved females. The age range was 3 months to 89 years; 60 per cent of patients were under 50 years old. Nearly half of the patients suffered permanent injury of varying degree and 15 patients died following treatment. Ten deaths were attributed to overwhelming sepsis, often as a result of peritonitis after open or laparoscopic abdominal surgical procedures. The 28 cases settled in 1999 revealed many similar problems to the seven completed in 1990, albeit in greater frequency. Claims arising from minimal access procedures first arose after 1991.

Reason for claim

The commonest reason for compensation was damage to underlying structures (32 per cent), a figure similar to that noted in an 8-year review first performed in 1998[3]. There were many other reasons for claim settlement and these are summarized in *Fig. 2*.

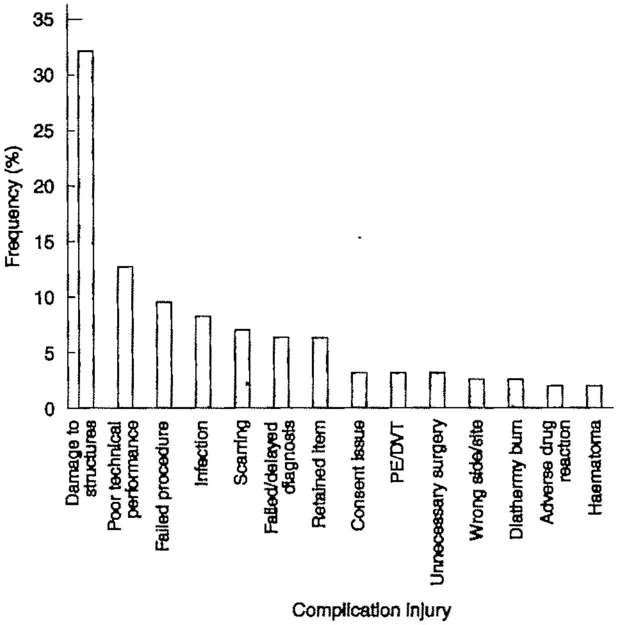

Fig. 2 General and vascular surgery claims settled by The Medical Defence Union in the UK from 1990 to 2000: complication/injury. PE, pulmonary embolism, DVT, deep vein thrombosis

All operations carry inherent risk to the patient, no matter how simple the procedure may seem. These risks are largely recognized and their existence should be made clear to patients as part of preoperative assessment. Many of the complications cited were eminently preventable and arose because of a failure to follow systems and checking procedures, or because of some intrinsic fault within the procedure itself. For example:

- issues of consent
- retained items
- surgery on the wrong side/site or wrong procedure
- unnecessary surgery
- electrodiathermy injury.

Rarely did a claim arise from a single issue; most involved a multiplicity of factors resulting in patient harm.

Conclusion

Examining claims for factors that lead to settlements highlights common and recurring themes. These include:

- communication failure, both between professionals and between doctor and patient

The MDU 2000

- inadequate clinical record keeping
- poor training and inadequate continuing professional development
- system failure.

Many risk factors, as seen from this simple review, can be identified from The MDU's data repository, but national trends are more difficult to determine because of a lack of published data. The importance of data sharing cannot be stressed too highly. A collaborative pooling exercise across the UK is essential if we are to reduce the potential for incidents that give rise to complaints and claims. Failure to learn lessons from often repeated themes will allow the rise in litigation to continue. Recognition of the risk associated with surgical procedures is an essential first step in implementing strategies to reduce such risk and improve patient safety.

References

1 Select Committee on Public Accounts. *Select Committee on Public Accounts Fifth Report. NHS (England) Summarised Accounts 1997–98.* www.publications.parliament.uk/pa/cm199900/cmselect/cmpubacc/128/12807.htm.

2 Morlock L, Mahtz F. Do hospital risk management programmes make a difference? *Law Contemporary Problems* 1991; **54:** 1–22.

3 Goodwin H. General and vascular surgery review. *Journal of the Medical Defence Union* 1999; **15:** 13–15.

The MDU 2000

The final product

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The completed manuscript – The Final Product – lies in front of you on your desk. What happens next? Do not be tempted to cram it rashly into an envelope and bear it with speed to the nearest post box. A moment's quiet contemplation at this point may avoid needless delay and embarrassment at a later stage when obvious, simple faults are uncovered by referees and editors.

Preparation of manuscripts

You will probably have had some idea of the journal to which your work might be sent for some time. Once a final selection has been made, sit down with the manuscript and the appropriate Instructions to Authors. These Instructions can be found in each issue of many journals and, if not, you will be pointed to a relevant issue or website by the Editorial Office of the publication concerned. Check your work carefully against the Instructions. It is surprising how many manuscripts have glaring, yet simple defects. These may result in a return of your work for revision even before peer review, typically entailing a delay of 2 weeks or more.

Authors should also consider the matter of English language spelling (English style or American style) and tailor their efforts appropriately. This should be straightforward in the present computerized era in which word processing spell-checkers are widely available for both styles. The point is especially relevant if submission is being made to a journal of second choice that uses spelling of a style different from that of the first choice publication. Journals can, of course, revise the spelling in-house and will rarely require authors to redraft on this count alone, but sending a manuscript in the 'wrong' style is lax at best and discourteous at worst.

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Many journals have correspondence pages; *BJS* is one such journal. Much correspondence relates to work that has recently been published in the journal and it is common practice for an editor to send any letter received about a paper to that paper's corresponding author. In this way the authors should be able to answer questions about their work raised by readers and to rebut criticism. A healthy correspondence section is the mark of a vibrant, successful journal. Editors will welcome your thoughtful and (again) speedy response to letters they have received.

Conclusion

The true 'final product' is, of course, your article published inside the pages of a prestigious journal. To reach this stage regularly you must work with speed and with care. Remember also that your text and letters are being sent into the public domain. Sign only that which you are confident about and encourage in your colleagues a similar degree of probity when dealing with editors and their publishers.

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Clinical dilemma

Soft tissue sarcoma involving the sciatic nerve

In the Clinical Dilemma slot the editors pose a question to an acknowledged expert in the field. In this issue we address the problem of a sarcoma in the posterior aspect of the thigh. At operation, despite preoperative magnetic resonance imaging, the lesion is unexpectedly found to involve the sciatic nerve. How should one proceed? Professor Murray Brennan of New York replies.

The patient, as presented, provides a considerable challenge. This event, however, should be rare or at least anticipated. In the evaluation of a posterior thigh mass with potential for involvement of the sciatic nerve, consideration should be given to the following factors. First, the presence of neurofibromatosis raises the significant possibility of a neurogenic tumour. Second, the size of the tumour is important: a lesion greater than 10 cm in diameter, situated deeply, has a far greater likelihood of involving the sciatic nerve than a smaller lesion[1]. Third, a preoperative biopsy will have been performed and some knowledge of the histopathology should have been gained. A malignant peripheral nerve tumour in close juxtaposition to the sciatic nerve raises the possibility of a primary origin from the nerve or nerve sheath[2]. Conversely, a low-grade liposarcoma, known by biopsy, is far less likely to involve the nerve or the nerve sheath and may be expected only to displace it. Finally, if the lesion is a high-grade tumour in close juxtaposition to the nerve, preoperative chemotherapy would have been considered already in an effort to improve resectability without sacrificing the nerve, and with the potential, but unproven, benefit of prolonging long-term survival.

Magnetic resonance imaging (MRI) has increased our ability to distinguish involvement of the sciatic nerve before surgery and so significant nerve involvement at operation, not appreciated by MRI, should be an uncommon event. But what of the actual dilemma? The involvement in this case is unsuspected. If it is assumed that the tumour is relatively small (less than 10 cm) and involvement of the nerve is minimal, as local recurrence alone is not a primary factor in survival, every endeavour should be made to preserve the nerve. It can be dissected from its sheath and, if the tumour is not truly of nerve origin, this should allow preservation of the nerve. Tumour-positive microscopic margins in this situation should be treated by radiation, either by brachytherapy or external-beam radiotherapy.

If there is a very large lesion of peripheral nerve and sciatic origin, not appreciated by preoperative MRI (definitely an uncommon situation), consideration of sacrifice of the nerve must be made. Historically, many physicians and surgeons have suggested that loss of the sciatic nerve is equivalent to an amputation. This is not true. Loss of the sciatic nerve results in the need for an ankle brace, and diligent attention to care of the insensate sole of the foot, and the inner skin of the foot and leg. Patients with this defect have a very functional leg, far superior to anything provided by amputation.

In summary, nerve involvement as outlined should rarely be unexpected. Modern preoperative imaging should define this potential difficulty. Preoperative biopsy for histopathological examination should further predict the likelihood of nerve involvement. When the tumour is large, the patient may often be treated with preoperative chemotherapy and, occasionally, preoperative radiotherapy. However, if, for whatever reason, unexpected nerve involvement is encountered at the time of operation, the action to be taken depends on the extent of involvement. Adherence should be treated with preservation of the nerve and postoperative radiotherapy[3], whereas frank involvement, invasion, or origin from the nerve mandates consideration of nerve resection. Preoperative discussion with the patient about the possibility of nerve division, with its consequent sensory and motor loss, is essential.

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Review

Portal flow augmentation for liver cirrhosis

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Background: Portal hypertension due to chronic liver disease is a major cause of death worldwide. Orthotopic liver transplantation offers the best therapeutic option but is available to only a minority of patients. In the past few years mechanically pumping portal venous inflow has been reported to reduce portal hypertension and improve liver function.

Methods: A review of the published data on augmented portal perfusion for the treatment of portal hypertension in cirrhosis was carried out by searching Medline and other online databases. From each published study portal pressure and blood flow data before and after augmented portal perfusion were used to calculate the change in mean intrahepatic portal vascular resistance (IHPR). The standardized data were then combined to allow meta-analysis.

Results: Seven papers were identified on normal and cirrhotic animal and human livers with augmented flow (50% to fourfold over baseline) for 30–180 min. Meta-analysis revealed that the increased portal venous inflow was associated with a significant rise in portal venous pressure on the hepatic side ($P < 0.001$), a significant reduction on the mesenteric side ($P < 0.001$) and a significant reduction in IHPR ($P = 0.013$). Limited data were available to support improved liver function.

Conclusion: Detailed *in vivo* cirrhotic liver studies on augmented portal flow in experimental models assessing haemodynamic and functional changes are required before clinical evaluation.

Paper accepted 22 March 2000

British Journal of Surgery 2000, 87, 984–991

Introduction

Over the past decade evidence has accumulated to suggest that enhancing the portal venous inflow in cirrhosis by use of a mechanical pump reduces portal venous pressure and intrahepatic portal vascular resistance (IHPR), thereby improving liver function. This study is a critical appraisal of the data published on this technique, with particular reference to hepatic haemodynamics and function.

In 1991, Habib *et al.*[1] first introduced the concept of enhancing portal blood flow in cirrhosis. In a porcine model with portal hypertension due to partial portal venous ligation, a mechanical increase in portal venous blood flow *in vivo* produced a decrease in portal pressure[1]. This preliminary finding in two animals was supported by data from perfusion of isolated cirrhotic rodent livers. With bench perfusion of isolated cirrhotic rat livers, Cardoso *et al.*[2] in 1993 subsequently suggested a decrease in intrahepatic resistance. Such augmented portal inflow has been found to increase parenchymal perfusion and is not due to intrahepatic shunting[2,3]. Functional improvement with portal flow augmentation was first suggested by Cardoso *et al.* by using drug clearance *in vitro* in isolated perfused cirrhotic livers[4] and *in vivo* in human cirrhotic livers before explantation for orthotopic liver transplantation (OLT)[5]. Bernadich *et al.*[6] addressed the effects of mechanical portal pumping on hepatic and systemic haemodynamics in rats with portal hypertension following portal vein stenosis. Portal flow augmentation decreased the portal pressure and portasystemic shunting without a significant effect on systemic haemodynamics[6,7].

This background experimental work has provided evidence from a variety of model systems to suggest that portal flow augmentation may be of potential therapeutic benefit in patients with portal hypertension from cirrhosis. Although the practical difficulties of applying this technique clinically may seem prohibitive, a working prototype of a fully implantable mechanical pump for insertion into the human portal vein has been designed and manufactured[7,8] (*Figs 1* and *2*). This is a review of the published experimental studies on portal flow augmentation in cirrhosis; its aim is to establish if hepatic haemodynamics and function are

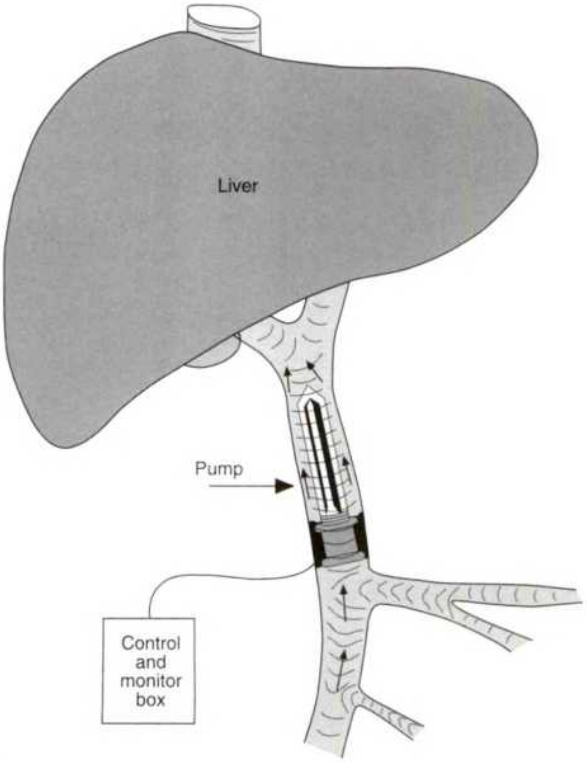

Fig. 1 Schematic diagram of an implantable impeller pump designed for insertion into the human portal vein

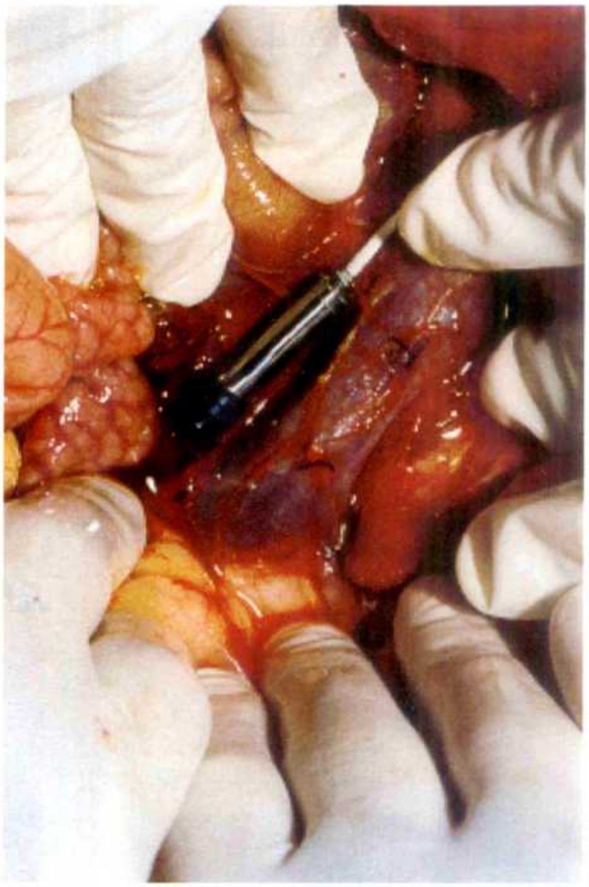

Fig. 2 Operative view of the implantable impeller pump adjacent to the portal vein in a porcine study of augmented portal perfusion

significantly improved. The following specific questions are addressed. (1) Are portal venous pressure and IHPR truly decreased? (2) Is liver function improved following a period of enhanced portal flow? (3) Does mechanically augmented portal perfusion result in deleterious effects on hepatocytes and liver architecture?

Methods

The work considered in this paper comprises all studies identified by Medline and internet search from 1970 to 1999 with the keywords 'pump', 'cirrhosis', 'portal hypertension' and 'hepatic flow'. Data analysis and statistical treatment were as follows. From each published study the experimental model was identified along with the baseline splanchnic haemodynamic data (portal pressure and flow rate). The increase in portal flow rate with pumping was recorded along with its duration. Pressure above and below the pump was identified, and liver function and histological assessment were recorded in each study at baseline and following augmented flow. In each study, where appropriate data were available, the mean IHPR was calculated from the pressure and flow data according to the following formula[7]:

$$\mathrm{IHPR} = P/Q$$

where P is the pressure in the portal vein between the pump and liver (measured in millimetres of mercury) and Q is portal blood flow (in millilitres per minute). In the *in vivo* studies the IHPR was measured from the portal vein pressure recorded following removal of the pump except in the study by Habib *et al.*[1] where pressures were taken above and below the pump

Data are presented as mean(s.d.). Statistical evaluation for comparison of IHPR, portal venous pressure and liver function before and after portal pumping in each individual study was made using a two-sample t test. For quantitative analysis of the combined results from each publication[9], a meta-analysis programme was used (Meta-analysis: version II; Dr D. A. Kenny, Department of Psychology, University of Connecticut, Storrs, Connecticut, USA). P values were weighted with both sample sizes and square rooted. $P < 0.05$ was taken as statistically significant.

Table 1 Published portal pumping studies

Reference	Year	Model	*n*	Method of assessment	DEPF (min)
Habib *et al.*[1]	1991	Cirrhotic rats	6	*In vitro*	n.a.
		Portal hypertensive pigs	2	*In vivo*	n.a.
Cardoso *et al.*[4]	1994	Cirrhotic rats	13	*In vitro*	60
Cardoso *et al.*[2]	1993	Cirrhotic rats	30	*In vitro*	60
Cardoso *et al.*[3]	1994	Cirrhotic human livers	6	*In vitro*	120
Cardoso *et al.*[5]	1994	Cirrhotic human livers	13	*In vivo*	30
Bernadich *et al.*[6]	1996	Portal hypertensive rats	10	*In vivo*	n.a.
Jiao *et al.*[7]	1999	Cirrhotic rabbits	6	*In vivo*	180

DEPF, duration of enhanced portal flow; n.a., data not available

Table 2 Studies analysing the haemodynamic effect of portal flow augmentation

				Baseline			Enhanced portal flow			
Reference	Year	Species	*n*	PVP (mmHg)	PVF (ml/min)	IHPR (mmHg.min/ml)	PVP_1 (mmHg)	PVP_2 (mmHg)	PVF (ml/min)	IHPR (mmHg.min/ml)
In vitro										
Habib *et al.*[1]	1991	Rat	6	9·6(1·8)	1·6(0·3)	6·00	33·1(0·0)*	n.a.	4·5(1·2)*	7·36
Cardoso *et al.*[4]	1994	Rat	13	8·3(0·9)	1·0(0·2)	8·30	11·4(1·6)†	n.a.	2·0(0·8)*	5·70
Cardoso *et al.*[2]	1993	Rat	30	11·5(1·8)	2·5(0·6)	4·60	23·3(1·4)*	n.a.	4·4(0·9)*	5·30
Cardoso *et al.*[3]	1994	Human	6	23·5(7·0)	651·7(73·1)	0·04	37·3(16·7)	n.a.	1254·1(134·6)*	0·03
In vivo										
Habib *et al.*[1]	1991	Pig	2	22·7(1·2)	454·0(42·0)	0·05	27·9(2·5)	19·1(1·0)	561·0(13·0)	0·03
Cardoso *et al.*[5]	1994	Human	13	31·8(5·3)	800·0(270·0)	0·04	n.a.	23·0(4·3)*	2400·0(1131·4)*	0·01‡
Bernadich *et al.*[6]	1996	Rat	10	18·0(1·0)	1·0(0·0)	18·00	n.a.	13·0(1·0)*	3·0(0·0)‡	4·33*
Jiao *et al.*[7]	1999	Rabbit	6	13·0(3·6)	52·4(24·6)	0·32(3·60)	n.a.	2·5(1·1)*	88·0(24·7)*	0·04(0·03)*

Values are mean(s.d.). PVP, portal venous pressure; PVP_1, portal inflow pressure; PVP_2, splanchnic portal pressure; IHPR, intrahepatic portal vascular resistance; n.a., data not available. $^*P \leq 0{\cdot}001$, $^†P = 0{\cdot}002$, $^‡P < 0{\cdot}05$ *versus* baseline (two-sample *t* test)

Results

Seven published studies were identified related to portal flow augmentation in portal hypertension[1–7] (*Table 1*), six of which were from the same group[1–5,7].

Experimental methods

There were four *in vitro* studies, three on cirrhotic rat livers[1,2,4] and one on explanted cirrhotic human livers[3]. Of the four *in vivo* studies, one analysed normal rat livers[6], one cirrhotic rabbit livers[7], one pig livers with portal hypertension induced by stenosis of the portal vein[1], and one human cirrhotic livers before explantation for OLT[5]. In all rodent models of cirrhosis portal hypertension was established with carbon tetrachloride. For *in vitro* bench perfusion, the livers were prepared with standard techniques[10] and perfused with Krebs–Ringer bicarbonate buffer solution[1–4,6]. Partial ligation of the portal vein was used to induce portal hypertension mechanically without cirrhosis in two *in vivo* animal experiments[1,6]. A portaportal shunt established by cannulating the proximal and distal part of the portal vein with an extracorporeal circuit[6], the use of a pneumatic pump[1] and a unidirectional extracorporeal pump[5], were used in four *in vivo* experiments. The duration of augmented portal blood flow varied from 30 to 180 min.

Hepatic haemodynamics

In all studies, both *in vitro* and *in vivo*, human and animal, portal inflow was increased from 50% to fourfold over the baseline flow. In cirrhotic rodents, portal venous pressure ranged from 8·3(0·9) to 11·5(1·8) mmHg (*Table 2*). This measurement was used in the bench perfusion experiments on isolated cirrhotic livers as the baseline portal venous pressure before portal flow augmentation. A subsequent twofold increase in portal venous flow over the baseline

Table 3 Liver function following augmented portal flow in cirrhosis

	In vitro			*In vivo*	
Variables	Cardoso *et al.*[4] (*n*=13, rats)	Cardoso *et al.*[2] (*n*=30, rats)	Cardoso *et al.*[3] (*n*=6, human)	Cardoso *et al.*[5] (*n*=5, human)	Jiao *et al*[7]. (*n*=6, rabbit)
Baseline					
Bile flow (µl/min)	11·0(1·7)	0·8(0·1)	157·8(15·7)		
Oxygen consumption (µmol/min)	27·5(2·7)		570·7(259·0)		
Intrahepatic shunt (%)	1·1(0·5)				
Liver function tests					
Bilirubin					
Aspartate aminotransferase					41 ± 25·9
Alanine aminotransferase		4·3(1·7)	31·0(31·7)		135·5 ± 52·3
Lactate dehydrogenase	0·2(0·1)				2030 ± 796·3
Drug extraction					
Taurocholate (ml/min)	0·67(0·07)				
Propranolol (ml/min)	0·88(0·03)				
Drug clearance					
Taurocholate (ml/min)	14·10(1·50)				
Propanolol (ml/min)	18·80(0·70)				
ICG extraction ratio			0·11(0·07)	0·15(0·09)	
ICG clearance (l/min)			86·0(58·3)	122·0(10·0)	
Enhanced portal flow					
Bile flow (µl/min)	10·4(1·6)	0·8(0·1)	153·8(32·9)		
Oxygen consumption (µmol/min)	30·5(4·5)		595·9(305·2)		
Intrahepatic shunt (%)	2·0(1·3)				
Liver function tests					
Bilirubin					
Aspartate aminotransferase					10.0 ± 5·9
Alanine aminotransferase		10·2(5·7)	37·7(37·7)		56·3 ± 19·8
Lactate dehydrogenase	0·4(0·1)				1309 ± 431·6
Drug extraction					
Taurocholate (ml/min)	0·66(0·07)				
Propranolol (ml/min)	0·82(0·05)				
Drug clearance					
Taurocholate (ml/min)	27·10(2·90)*				
Propanolol (ml/min)	33·40(2·00)*				
ICG extraction ratio			0·08(0·05)*	0·09(0·06)†	
ICG clearance (l/min)			109·2(74·8)*	150·0(120·0)†	
Variance (%)					
ICG extraction			−28(13)	−33(15)	
ICG clearance			28(23)	32(27)	
Taurocholate clearance	50				
Propranolol clearance	60				

Values are mean(s.d.). ICG, indocyanine green. $^*P<0·05$, $^\dagger P=0·05$ *versus* baseline (two-sample *t* test)

using the portal pump was associated with an increase in inflow portal venous pressure varying from 11·4(1·6) to 33·1(0·0) mmHg ($P=0·002$ to $P<0·001$). Portal venous flow was significantly increased by portal flow augmentation in all studies but one (*Table 3*); in which the increase was not statistically significant. Portal venous pressure on the mesenteric side of the pump was significantly reduced with augmentation of portal flow in three of four studies, showing a significant reduction in one study on human cirrhotic liver ($P<0·001$), one study on normal rat liver with portal hypertension ($P<0·001$), and one with cirrhotic rabbit liver ($P<0·001$).

The IHPR was calculated using the published flow and pressure data; only three studies showed a significant reduction following portal flow augmentation (*Table 2*). One study analysed intrahepatic shunting and found no significant alteration in cirrhotic livers following portal pumping[4] (*Table 3*). Meta-analysis of published data, both *in vitro* and *in vivo*, revealed that a significant increase in the portal venous inflow was associated with a significant rise in portal venous pressure on the hepatic side ($P<0·001$) and a reduction in portal venous pressure on the mesenteric side ($P<0·001$). IHPR was also significantly reduced ($P=0·013$) (*Table 4*).

Table 4 Meta-analysis of the published studies, both *in vitro* and *in vivo*

	Hepatic haemodynamics				Liver function	
	PVP_1 (mmHg)	PVP_2 (mmHg)	PVF (ml/min)	IHPR (mmHg.min/ml)	S_e (ml/min)	S_{cl} (ml/min)
N	63	31	86	86	35	35
*P**	<0·001	<0·001	<0·001	0·013	0·04	<0·001

PVP_1, portal venous pressure on the hepatic side; PVP_2, portal venous pressure on the splanchnic side; PVF, portal venous flow; IHPR, intrahepatic portal vascular resistance. S_e, substance extraction; S_{cl}, substance clearance. **Versus* baseline

Systemic haemodynamics

The effect of portal pumping on systemic haemodynamics was assessed in three studies[5–7]. No significant alteration was detected in mean arterial pressure, central venous pressure, total peripheral vascular resistance, cardiac index and renal blood flow.

Liver function

Four studies assessed liver function, two of them *in vitro*, one on cirrhotic rat liver and one on cirrhotic human livers[3,4]. Two studies have been undertaken *in vivo*[5–7], one examined liver function improvement in human cirrhotic livers before explantation for OLT after 30 min of mechanical pumpings and the other assessed standard liver function tests following 180 min of augmented portal flow[7]. Clearance of propranolol and taurocholate in cirrhotic rodent livers and of indocyanine green in cirrhotic human livers was used to determine hepatic drug extraction and elimination as a reflection of liver function before and after enhancing portal inflow. Both animal and human studies demonstrated an increase in drug clearance by 28–60 per cent following portal pumping (*Table 3*). Bile flow, oxygen consumption, and production of lactate dehydrogenase and alanine transaminase were not significantly altered following bench portal venous augmentation in cirrhotic rodent and human livers.

Both substance extraction and clearance were significantly improved ($P = 0{\cdot}040$ and $P < 0{\cdot}001$ respectively) with enhanced portal inflow (*Table 4*).

Hepatocytes and liver architecture

All *in vitro* studies monitored macroscopic liver appearance during enhanced portal flow and histology after perfusion. Histological examination of livers after augmented portal blood flow showed no evidence of structural damage from mechanical force. In all studies reported by Cardoso *et al.* sinusoidal dilatation was reported in both *in vivo* and *in vitro*. During perfusion, 'weeping of ascitic like fluid' was observed in several studies[2,3] but the precise quantity and nature of this fluid was not assessed.

Discussion

This meta-analysis has combined and analysed the data from several publications, but the number of these publications is small and all but one come from the same group of investigators. There are many differences in study design, suggesting a need for caution when comparing the results.

Experimental animal models of cirrhosis induced with carbon tetrachloride offer both histological and haemodynamic features similar to those of human cirrhosis[11–13]. The cirrhotic rodent livers used in the portal pumping studies were in this respect satisfactory, showing histological evidence of cirrhosis characterized by the presence of regenerating cirrhotic nodules and a raised portal venous pressure. A raised intrahepatic vascular resistance and increased splanchnic blood flow are the principal factors producing portal hypertension in cirrhosis[14]. Unlike the chemical-induced cirrhotic model, animal models of portal hypertension established by portal vein stenosis do not show the haemodynamic and functional changes associated with cirrhosis, although there is portal hypertension. The portal vein stenosis model is not, therefore, representative of the haemodynamic changes in cirrhosis.

In isolated cirrhotic rat livers, the hepatic haemodynamic variables are altered from those found *in vivo*. Portal venous flow is set by a mechanical pump which will in turn influence the pressure proximal and distal to the pump. The normal relationship between portal venous and hepatic arterial flow is no longer valid[15–17]. Four of the eight reported studies used bench perfusion of isolated cirrhotic livers. The portal perfusion achieved in these bench studies reached up to fourfold above the baseline portal venous blood flow in cirrhotic rodents. In normal physiology, the amount of blood returned to the portal vein from the splanchnic circulation is constant[18]. A sudden fourfold increase in portal venous inflow *in vivo* by mechanical pumping is probably not feasible in practice, a view supported by recent work in the authors' laboratory using a normal porcine model. In cirrhosis, although there is hyperaemia in the splanchnic circulation, the amount of portal venous blood available for portal pumping is limited. An increase of up to 50 per cent over the baseline portal flow could be achieved without an acute reduction in the venous supply in cirrhotic rabbits[7].

An increase in the portal blood flow in cirrhotic livers was associated with an increase in portal inflow pressure and a reduction in splanchnic portal pressure in all studies. Systemic haemodynamic data showed that mechanically increasing the portal inflow had no effect on the systemic circulation, indicating that there was no systemic compensatory response from augmented portal inflow. In portal hypertension, the appearance of ascites in patients with cirrhosis carries a poor prognosis. The probability of surviving 5 years after the first episode of ascites has been estimated at 20 per cent[19,20]. When renal failure coexists, the majority of patients die within weeks or months from this cause[21,22]. An increase in the intrahepatic hydrostatic pressure from portal pumping may accelerate the production of ascites as suggested by *in vitro* bench studies[2,4]. This issue has not been addressed adequately in the published studies. Alternatively, an increase in intrahepatic portal pressure may actually be beneficial by promoting diffusion of substances through the sinusoids. The reduction in splanchnic pressure may reduce pressure in collaterals, thereby reducing bleeding from oesophageal varices. Portal pressure reduction in collaterals is known to correlate well with the risk of variceal haemorrhage[23].

Intrahepatic portal resistance is dependent on portal pressure and blood flow, as expressed in effect by Ohm's law. Using the published flow and pressure data, this meta-analysis has demonstrated a significant reduction in IHPR with augmented portal flow. However, this was not evident in all *in vitro* studies, despite the authors' claims in their original publications[1–4]. The hepatic circulation is regulated by both intrinsic and extrinsic factors[24]. In the denervated isolated liver, portal vascular resistance measurements fail to take into account the hepatic blood volume[25], sympathetic and other neurohumoral influences[26], cardiac influences on splanchnic circulation[27], and the inverse relationship between portal and hepatic arterial blood flow[28]. Under these circumstances, it is difficult to elicit the real effects of portal pumping on hepatic haemodynamics. The precise mechanism by which a short-term enhanced portal venous flow was associated with a significant reduction in IHPR has not been examined. Both the amount of fibrosis and the vascular tone have been reported to determine the total portal vascular resistance[29]. As fibrosis is unlikely to be influenced by short-term augmented portal inflow, it would seem likely that the change in vascular resistance is related to altered vascular tone. Dilatation of sinusoidal spaces was found in some liver biopsies by Cardoso *et al.*[2]. This supports the IHPR being reduced owing to vasodilatation following enhancement of portal blood flow, based on Poiseulle's law, which states that the resistance to blood flow varies directly with the length of the blood vessel and viscosity of the blood, and inversely with the fourth power of the radius. In addition, it is increasingly recognized that various intrinsic vasodilators may play an important part in regulation of portal vascular resistance[30]. With an increased mechanical shear force, there may be increased release of endothelin with an associated release of vasodilator agents such as nitric oxide[31]. However, this hypothesis remains to be tested.

The effect of portal flow augmentation on liver function has been addressed in a limited way in a few studies[2–4,5,7]. In cirrhosis, there are features of capillarization and collagenization[32–34] that can result in impaired exchange of substances within the space of Disse. *In vitro* augmented perfusion of cirrhotic rat livers increased drug elimination, although a much lower extraction of substances in isolated livers has been reported compared with that of livers in anaesthetized animals or humans[15–17]. Enhancing hepatic blood flow *in vivo* increases the delivery of drugs to the liver and the hydrostatic pressure across the space of Disse. This may lead to an increase in drug elimination from cirrhotic livers, but may not reflect improved hepatocyte uptake and metabolism[35]. Drug clearance has been shown to improve significantly following a period of augmented portal perfusion[3]. This has been attributed to an increase in hydrostatic pressure within the vascular space and forced drug diffusion through the altered sinusoid wall. The mechanism has not been investigated. Recently, enhancing the portal inflow mechanically has been shown to increase the hepatic microcirculation and improve tissue oxygenation. This has led to improvement in liver function as assessed by standard biochemical tests of liver function[19]. Although previous studies[5] suggested improvement in liver function by measuring hepatic indocyanine green clearance in human cirrhotic livers, a 4–6-min period of augmented portal inflow is unlikely to reverse the biochemical abnormalities associated with damaged hepatocytes. This suggests that enhancing portal inflow simply increases hepatic uptake and clearance of indocyanine green[36].

Although histological examination has shown no damage to the liver architecture using trypan blue assessment and electron microscopy after augmentation of portal flow[2], long-term effects on the hepatic parenchymal structure and the adjacent organs have not been investigated. Long-term augmented flow studies are required.

Meta-analysis was used in this study to process all published data in relation to portal pumping and its effect on hepatic haemodynamics and liver function. This has enabled the results of several studies to be 'combinable'[9]. Review of the data from previously published studies on portal flow augmentation in cirrhosis has highlighted the variety of study designs. Despite this heterogeneity, a strong correlation between augmented portal perfusion and both decreased hepatic vascular resistance and reduced splanchnic pressure has been demonstrated. Future *in vivo* experimental studies are required to define the short- and long-term haemodynamics *in vivo*, functional changes to the liver parenchyma and the effects of portal pump implantation in the longer term. These results are essential for establishing the validity of the concept that portal flow augmentation may be a useful therapeutic modality in cirrhotic portal hypertension.

Acknowledgements

The authors acknowledge the support of EU (ESPRIT IV Grant no. 21245) for L.R.J.

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E-cadherin–catenin cell–cell adhesion complex and human cancer

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Background: The E-cadherin–catenin complex plays a crucial role in epithelial cell–cell adhesion and in the maintenance of tissue architecture. Perturbation in the expression or function of this complex results in loss of intercellular adhesion, with possible consequent cell transformation and tumour progression. Recently, much progress has been made in understanding the interaction between the different components of this protein complex and how this cell–cell adhesion complex is modulated in cancer cells.

Methods: This is an update of the role of the E-cadherin–catenin complex in human cancers. It emphasizes new features and the possible role of the complex in clinical practice, discussed in the light of 165 references obtained from the Medline database from 1995 to 1999.

Results: More evidence is now appearing to suggest that disturbance in protein–protein interaction in the E-cadherin–catenin adhesion complex is one of the main events in the early and late steps of cancer development. An inverse correlation is found between expression of the E-cadherin–catenin complex and the invasive behaviour of tumour cells. Therefore, E-cadherin–catenin may become a significant prognostic marker for tumour behaviour. Besides its role in establishing tight cell–cell adhesion, β-catenin plays a major role in cell signalling and promotion of neoplastic growth. This suggests its dual role as a tumour suppressor and as an oncogene in human cancers.

Conclusion: Recent developments show that the E-cadherin–catenin complex is more than a 'sticky molecular complex'. Further studies may yield greater insight into the early molecular interactions critical to the initiation and progression of tumours. This should aid the development of novel strategies for both prevention and treatment of cancer.

Paper accepted 22 March 2000

British Journal of Surgery 2000, 87, 992–1005

Introduction

It has long been known that cell–cell adhesion is generally reduced in human cancers. Reduced cell–cell adhesiveness is associated with loss of contact inhibition of proliferation, thereby allowing escape from growth control signals[1]. Invasion and metastases, the most life-threatening properties of malignant tumours, are considered to be later, but critically important, carcinogenic steps. These steps consist of sequential changes in host–tumour interaction. The suppression of cell–cell adhesiveness may trigger the release of cancer cells from the primary cancer nests and confer invasive properties on a tumour. In order for a metastatic nodule to form, cancer cells must detach from the primary site, invade through the surrounding host tissue, enter the circulation, lodge in a distant vascular bed, extravasate into the target organ, and proliferate[2]. Reduced cell–cell adhesiveness is considered indispensable for both the early and the late carcinogenic steps. In recent years, there has been increasing interest in a large family of transmembrane glycoproteins, called cadherins, which are the prime mediators of calcium-dependent cell–cell adhesion in normal cells[3]. There is increasing evidence that modulation of this complex by different mechanisms is an important step in the initiation and progression of human cancers.

Cadherins

The cadherins have been divided up into more than 10 subclasses, depending on their tissue distribution; these include E- (epithelial), N- (neuronal) and P- (placental) cadherins[4,5]. E-cadherin (120 kDa; chromosome 16q), otherwise known as uvomorulin, L-CAM, cell-CAM 120/80 or Arc-1, is a classical cadherin and forms the key functional component of adherens junctions between epithelial cells[6]. Normal E-cadherin expression and function are essential for the induction and maintenance of polarized and differentiated epithelia during embryonic development[3]. The critical importance of E-cadherin in normal development and tissue function is demonstrated by the lethality of E-cadherin knockout mice at an early stage in embryogenesis[7]. The binding of cadherins is homotypic in nature, i.e. they bind only to identical molecules on adjacent cell surfaces. The contribution of cadherins to intercellular binding is achieved through the formation of cell surface multimolecular structures with a 'zipper' confirmation[8].

Catenins

Cadherin binding requires a complex series of interactions between cadherins and cytoplasmic molecules. E-cadherin is bound via series of undercoat proteins, the catenins, to the actin cytoskeleton[9] (*Fig. 1*). This linkage between transmembranous cadherins and actin filaments of the cytoskeleton is necessary to form strong cell–cell adhesion[10]. Deletion of the intracellular catenin-binding domain of E-cadherin or alteration of the functionally active catenins results in loss of the ability of E-cadherin to establish cell–cell adhesion, even if the extracellular binding domain is intact[10]. The catenin family comprises α- (102 kDa, chromosome 5q21–22)[11], β- (92 kDa; chromosome 3p22)[12] and γ- (plakoglobin; 83 kDa; chromosome 11q11)[13] catenins, with β- and γ-catenin sharing the greatest homology. β-Catenin and γ-catenin bind directly to the cytoplasmic tail of E-cadherin in a mutually exclusive manner; α-catenin then links the bound β- or γ-catenin to the actin microfilament network of the cytoskeleton. Recently, another catenin-like molecule, $p120^{ctn}$, has been identified in association with E-cadherin at the cell–cell junctions, although this complex does not appear to form a link with the actin cytoskeleton[14]. Originally identified as one of the several substrates of tyrosine kinase pp60src, $p120^{ctn}$ also associates with β-catenin and E-cadherin[15]. Unlike the other catenins, it has four isoforms, which appear to be expressed differentially in a variety of cell types[14]. Recently, it has been shown that $p120^{ctn}$ acts as an inhibitory regulator of cadherin function in colon carcinomas[16].

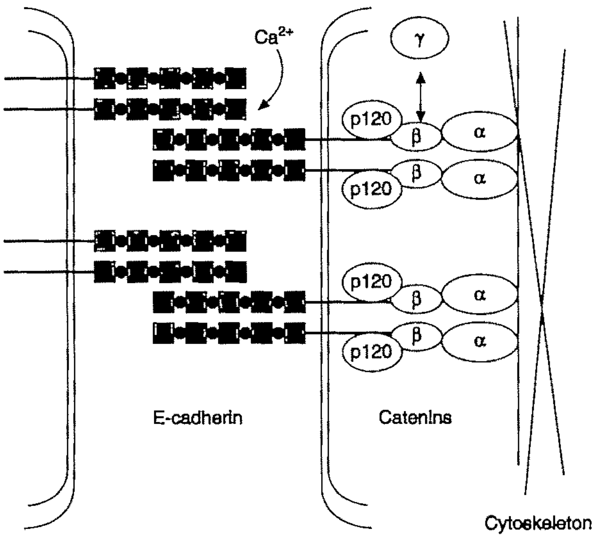

Fig. 1 Schematic representation of cadherin-mediated cell–cell adhesion in epithelial cells. Intercellular binding is achieved through the formation of E-cadherin dimers that interdigitate to form a continuous linear 'zipper' structure. The interaction is dependent on extracellular calcium levels. The cytoplasmic domain of E-cadherin is complexed with either β- or γ-catenin. α-Catenin links the complex to the actin cytoskeleton of the cell

E-cadherin–catenin complex in tumour development

An intact E-cadherin–catenin complex is required for maintenance of normal intercellular adhesion. In the light of this, several groups have proposed that in carcinomas E-cadherin functions as an invasion suppressor molecule such that its loss permits or enhances the invasion of adjacent normal tissues. There are many data to support this hypothesis. Immunohistochemical studies in human cancers have frequently shown that a proportion of invasive carcinomas and carcinomas *in situ* show aberrant levels of E-cadherin and/or catenin expression in comparison to their related normal tissue[17–19]. In general, E-cadherin and catenin staining is strong in well differentiated cancers that maintain their cell adhesiveness and are less invasive, but is reduced in poorly differentiated tumours which have lost their cell–cell adhesion and show strong invasive behaviour. Changes in E-cadherin expression may, therefore, be an important step in the development and progression of a malignant tumour. *In vitro* studies have shown various human cancer cell lines with an epithelioid, differentiated morphology to be generally non-invasive and to express E-cadherin, whereas cell lines with a fibroblast-like morphology are invasive and have often lost E-cadherin expression[20]. Reconstruction of cadherin binding in human carcinoma cell lines by transfection with E-cadherin complementary DNA (cDNA) results in a more differentiated phenotype and loss of invasiveness[20–22]. Furthermore, non-transformed Madin-Darby canine kidney epithelial cells, as well as well differentiated colon carcinoma cell lines, acquire a dedifferentiated and invasive phenotype when intercellular adhesion is inhibited by anti-E-cadherin monoclonal antibodies[23,24]. This clearly demonstrates that E-cadherin can suppress the overt features of advanced tumour progression. However, it remains unsolved whether the loss of E-cadherin-mediated cell adhesion is a prerequisite for tumour progression or is a consequence of dedifferentiation during tumour progression *in vivo*. This question was recently addressed using a transgenic mouse model of pancreatic β-cell tumorigenesis. Perl *et al.*[25] demonstrated that the loss of E-cadherin-mediated cell–cell adhesion is causally involved in the transition from adenoma to invasive carcinoma.

Loss of cadherin-mediated adhesion may also act by promoting tumour cell detachment from the primary site, resulting in dissemination of malignant cells to distant organs. Direct evidence implicating E-cadherin in the development of metastases is based on the association between highly metastasizing carcinomas and low E-cadherin immunoreactivity[26,27]. An *in vitro* study has shown that E-cadherin-negative tumour cells are more likely than E-cadherin-positive cells to be dislodged from the primary tumour by low shear forces, such as these found in venules or the lymphatic system[28]. The involvement of E-cadherin in metastasis was studied using an *in vivo* model of nude mice[29,30]. Injection of E-cadherin-negative breast cancer cells into the circulation gave rise to multiple lung and osteolytic bone metastases in these mice. However, breast cancer cells that were transfected with E-cadherin cDNA showed a significantly impaired capacity to form osteolytic metastases[29]. It is also known that patients with breast cancer whose tumours have reduced E-cadherin expression have a higher frequency of lymph node and distant organ metastases than those whose tumours have preserved E-cadherin expression[27].

E-cadherin as a growth suppressor

It has recently become clear that E-cadherin is involved in contact inhibition of cell growth by inducing cell cycle arrest[1,31]. Sequential activation and inactivation of a family of cyclin-dependent kinases govern the cell cycle. One such cyclin-dependent kinase inhibitor is *p27*, which results in cell cycle arrest; it is now established that E-cadherin has the ability to inhibit cell proliferation by the upregulation of p27[1], although the mechanism by which E-cadherin regulates p27 is still unclear. Inhibiting the activity of mitogenic pathways, perhaps via the epidermal growth factor (EGF) receptor (EGFR), which in turn regulate the level of p27 in cells is suggested. Therefore, E-cadherin, generally described as an invasion suppressor[21], is also a major growth/proliferation suppressor. This attractive model for E-cadherin might explain earlier findings by Hermiston *et al.*[32,33]. They showed that inactivation of E-cadherin in intestinal crypt cells leads to formation of adenomas, and that forced expression of E-cadherin suppresses proliferation.

Role of β-catenin in signal transduction

An important function of β-catenin, namely its role in cell signalling, has been elucidated in the past few years[34–36]. β-Catenin is the vertebrate homologue of the *Drosophila* segment polarity gene armadillo, an important element in the Wingless/Wnt (Wg/Wnt) signalling pathway. Wingless is a cell–cell signal in *Drosophila* that triggers many key developmental processes, Wnt being the vertebrate homologue[37]. In the absence of a mitotic signal from outside the cell β-catenin is sequestered in a complex with the adenomatous polyposis coli (APC) gene product, a serine threonine glycogen synthetase kinase (GSK-3β) and an adapter protein axin (or a homologue conductin), enabling phosphorylation and degradation of free β-catenin by the ubiquitin–proteasome system[38]. The function of and interactions between the proteins in the complex was something of a mystery until recently. Axin, a recently recognized component of the complex, acts as a scaffold protein in the multiprotein structure[39]. Formation of an axin regulatory complex is critical for GSK-3β activity and β-catenin phosphorylation and degradation, since GSK-3β does not bind directly to β-catenin but requires the presence of axin, which binds to both proteins[40]. This complex formation leads to the maintenance of low levels of free cytoplasmic β-catenin. Residual catenins hold cells together by binding to cadherins, both at the adherens junctions and the actin cytoskeleton.

When a mitotic signal is delivered by the Wnt pathway, by association of the Wg/Wnt family of secreted glycoproteins and their membrane receptor frizzled, it leads to activation of the dishevelled (Dsh) protein, which is recruited to the cell membrane. The activated Dsh downregulates the protein complex, so that it can no longer phosphorylate β-catenin, which then is not degraded[41]. How exactly Wnt signalling leads to the stabilization of β-catenin remains unclear, although it is suggested that that a critical step might be the dissociation of GSK-3β from axin with the help of Dsh[42]. With GSK-3β no longer bound to axin, it cannot phosphorylate β-catenin, leading to an increase in β-catenin levels. Another proposed model is that inhibition of GSK-3β activity upon Wnt signalling by Dsh leads to the dephosphorylation of axin, resulting in a

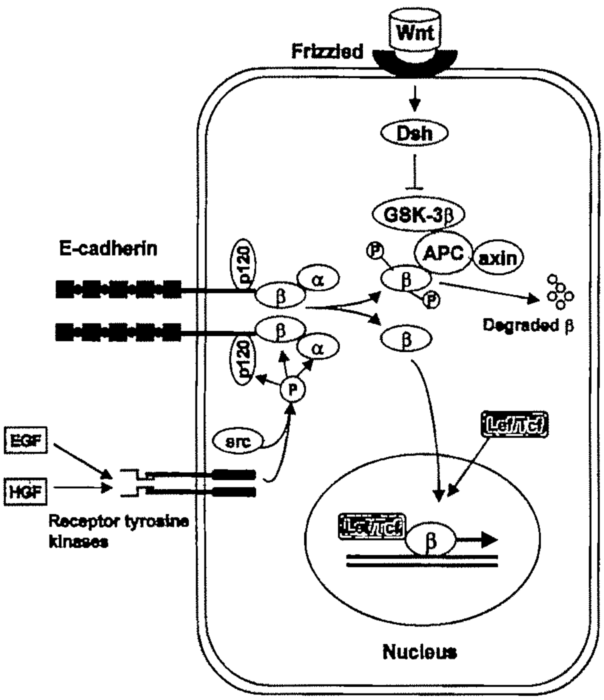

Fig. 2 Schematic representation of the catenins and the interaction with other transmembrane, cytosolic and nuclear proteins. The unbound cytoplasmic pool of β-catenin is sequestered in a protein complex and phosphorylated by glycogen synthetase kinase (GSK-3β, enabling its degradation. Abnormalities in this degradation pathway (activation of the Wnt pathway, mutated adenomatous polyposis coli (APC) gene product or mutated β-catenin) can lead to an increase in the level of free β-catenin, which then translocates to the nucleus, binds transcription factors (Lef/Tcf) and stimulates transcription of target genes. The catenins also interact with receptor tyrosine kinases, such as the epidermal growth factor (EGF) and hepatocyte growth factor (HGF) receptors, which alter their phosphorylation status and, as a consequence, modulate E-cadherin–catenin cell–cell adhesion. See text for details. Dsh, dishevelled

reduced efficiency of binding to β-catenin. The release of β-catenin from the phosphorylation and degradation complex promotes β-catenin stabilization and signalling[43,44]. The resulting increase in free cytosolic β-catenin then enters the nucleus. This results in an increase of free cystolic β-catenin which translocates to the nucleus and directly binds the transcription factors Lef and Tcf, leading to the activation of gene expression[45–47]. Recently, the target genes of these transcription factors have been identified. They are thought to be involved in inhibiting apoptosis and promoting cellular proliferation and migration, and include the c-*myc* oncogene and one of the cell cycle regulators cyclin D1[48–51]. γ-Catenin can also enter the nucleus and interact with these transcription factors, but γ-catenin has been shown to have transactivation capacities different to those of β-catenin, thus leading to distinct signalling properties[52].

Although β-catenin performs distinct functions in E-cadherin-mediated cell–cell adhesion and in Wnt signalling[53], there appears to be some cross-talk between the adhesive and signalling pathways. The expression of excess E-cadherin interferes with Wnt signalling by competing for β-catenin binding[54]. However, loss of cadherin binding does not lead to accumulation of β-catenin free to bind Tcf/Lef-1 and to modulate transcription[55]. Interestingly, Lef-1-β-catenin is also able to bind the E-cadherin promoter, possibly leading to downregulation of E-cadherin[56].

Activation of the Wg/Wnt pathway in human cancers

It is now believed that transformation of adult mammalian cells into malignant tumours reflects an exaggeration of the Wg/Wnt pathway, at least in some tumours. The *APC* gene is mutated in many cancers. In fact, it is supposed to be the first genetic alteration in the multistep process in inherited (familial adenomatous polyposis coli) and sporadic colorectal cancers[57]. Recently, it was found that APC regulates levels of free β-catenin in the cell, as discussed above. Most of the mutations in *APC* result in truncated APC protein which can still complex with, but not degrade, β-catenin[58]. The result of *APC* mutation is, therefore, an increase in cellular free β-catenin, which may trigger a cascade of events resulting in the initiation of adenomas[59]. *APC* mutations in colorectal cancers have been shown to result in an increase in β-catenin/Tcf-4 signalling, leading to overexpression of the c-*myc* proto-oncogene and promotion of neoplastic growth[48,60]. However, somatic mutations or small deletions (but no germline mutations) in the β-catenin gene, targeting the serine and threonine residues necessary for phosphorylation by GSK-3β and breakdown by the APC/GSK complex, are also associated with colon carcinogenesis[60,61]. These β-catenin mutations have a dominant effect, suppressing the APC-dependent binding and degradation of β-catenin, leading to accumulation of cytoplasmic free β-catenin, again with subsequent translocation of β-catenin to the nucleus.

In the past 2 years many studies have revealed that activation of the Wg/Wnt pathway by mutated β-catenin is a rather frequent event in malignancies, including hepatocellular and thyroid carcinomas, desmoid tumours and pilomatricomas[62–65], but uncommon in melanomas, head and neck cancers, and oesophageal and prostatic carcinomas[66–69]. This implicates β-catenin as an oncogene in cancer development, giving a possible explanation for the uncontrolled proliferation observed in cancers. Perhaps this is why widespread nuclear and cytoplasmic staining of β-catenin in colorectal cancers is an independent prognostic factor for short survival[70]. Similarly, mutations in GSK-3β, axin or other (yet unknown) elements involved in the Wnt/Wg pathway may contribute to β-catenin signalling. Future studies need to focus on these other components of the complex to elucidate the Wg/Wnt pathway in human cancers.

Mechanisms of inactivation of the E-cadherin–catenin complex in cancer

Human cancers possess both irreversible and reversible mechanisms for inactivation of the E-cadherin–catenin complex which lead to invasion and metastases. Loss of the E-cadherin locus on the long arm of chromosome 16 (16q22) occurs at rather high frequency in hepatocellular (50 per cent), lobular breast (50 per cent) and oesophageal (66 per cent) carcinomas[71–73]. There have been several reports on E-cadherin gene mutations in human cancers[74]. In poorly differentiated tumours, such as lobular breast cancer and diffuse-type gastric cancer, E-cadherin mutations play an important role in tumour development[75,76]. However, mutations are rare in oesophageal, thyroid and colorectal carcinomas[73,77,78]. Interestingly, E-cadherin mutations with loss of the remaining wild-type allele are also detectable in the preinvasive *in situ* component of lobular breast cancer and in intramucosal lesions of gastric signet ring cell carcinomas[79,80]. This, together with the findings of Perl *et al.*[25], indicates that genetic alterations of the E-cadherin gene are involved in the early developmental stages of some histological types of human cancer, and that both E-cadherin alleles are inactivated. The importance of loss of function of E-cadherin in the onset of cancer is now well established. Several studies have reported germline mutations in the E-cadherin gene in families with an inherited diffuse type of gastric cancer[81,82]. However, the clinical implications of these findings are not yet clear. Only a minority of gastric cancers can be accounted for by E-cadherin mutations. Recently, it has been recognized that early onset of lobular breast carcinoma may also be associated with E-cadherin germline mutation[82,83].

So far, mutations in the α-catenin gene have been described only for cell lines, not in tumours *in vivo*[84,85]. Human cultured cancer cell lines with a genetically altered α-catenin only regain their cell–cell adhesiveness when transfected with wild-type α-catenin cDNA[86]. Therefore α-catenin meets the criteria of an invasion suppressor gene.

Genetic alterations in β-catenin abolishing cell–cell adhesiveness have been observed in two gastric cancer cell lines, HSC 39 and 40A; both derive from the same signet ring cell carcinoma of the stomach and show a diffuse growth pattern[87,88]. This mutation results in a truncated β-catenin that lacks the region for interaction with α-catenin. Transfection of these cell lines with wild-type β-catenin restores cellular adhesiveness[88]. Recently, a mutation in γ-catenin has been described in a gastric cancer cell line, but no mutations have been reported in sporadic gastric cancers[55].

Downregulation of E-cadherin expression may be induced by a low activity of the E-cadherin promoter owing to chromatin rearrangement in the regulatory domain or to DNA methylation[89,90]. *In vivo* experiments show that methylation in the E-cadherin promoter region correlates significantly with reduced E-cadherin expression in hepatocellular carcinomas and methylation may also be detected frequently in precancerous conditions[91]. Furthermore, an *in vitro* experiment has shown that downregulation of E-cadherin by stimulating c-erbB2 transcription further reduces E-cadherin promoter activity, suggesting a role for c-erbB2 overexpression in tumour progression and metastases[92]. However, an immunohistochemical study has produced a strong argument against a role for c-erbB2 as a transcriptional regulator of E-cadherin expression in breast carcinomas *in vivo*[93]. In addition, downregulation of β-catenin in cholangiocarcinomas is associated with c-erbB2 downregulation[94]. EGFR and the tumour suppressor p53 may also play a role in the regulation of E-cadherin and α-catenin expression, and perturbation of the E-cadherin–catenin complex[95,96]. It is also known that *Helicobacter pylori* infection is associated with downregulation of E-cadherin in gastric mucosa and so might play a role in the onset of neoplastic growth[97].

In some tumours, including pancreatic, thyroid, gastric, bronchopulmonary, oesophageal, colorectal and bladder cancers, the staining pattern of the E-cadherin–catenin complex does not always indicate an absence or reduction in expression but shows a redistribution from the cell membrane to the cytoplasm[19,98–103]. The mechanism responsible for this redistribution in tumour cells remains elusive. Immunoprecipitation experiments have been performed to address this point, with modifications in the interactions between E-cadherin and the catenins being observed[98,104]. In colorectal tumours with heterogeneous cytoplasmic immunoreactivity for E-cadherin as well as the catenins, one of the catenins was not present in the complex, or the cytoskeletal bound fraction was reduced in spite of an overall increase in expression of the proteins (M. El-Bahrawy, personal communication)[99,105]. These studies have shown that the expression of the proteins does not necessarily imply that they are functioning; binding of the E-cadherin–catenin complex to the cytoskeleton is essential for its role in cell adhesion.

Failure of E-cadherin and catenins to localize to the membrane and/or bind to the cytoskeleton in spite of their abundant presence may be due to alterations in their phosphorylation status[100,101]. A number of receptor and non-receptor tyrosine kinases and phosphatases, including the EGFR, the c-*erbB2* oncogene and the hepatocyte growth factor receptor, c-met, interact with the catenins. This interaction alters the phosphorylation status of the catenins and, as a consequence, cadherin-mediated adhesion[106–110]. For example, EGFR has tyrosine kinase activity that is activated through autophosphorylation upon its binding to EGF. By this mechanism EGF induces immediate phosphorylation of β- and γ-catenin which is inhibited by herbimycine, a tyrosine kinase inhibitor[111]. Overexpression of EGFR, c-erbB2 and c-met has been described in several cancers. This was associated with cellular redistribution of E-cadherin from the membrane to the cytoplasm along with suppression of its function[111,112]. In addition, there is evidence to suggest that the association between E-cadherin and α-catenin can be prevented by tyrosine phosphorylated β-catenin[113].

Further evidence of the possible role of tyrosine phosphorylation as a mechanism by which E-cadherin–catenin function is modulated comes from findings in cells transfected with the v-*src* oncogene. Increased tyrosine phosphorylation of β-catenin and E-cadherin is observed and this post-translational modification results in functional changes, such as decreased cell–cell adhesion, increased migration and increased invasiveness, without affecting the overall expression of either of the catenins or the cadherins[114,115]. The inhibition of tyrosine phosphorylation restores cadherin function to normal[114]. Other studies show that upregulation of tyrosine phosphorylation of β-catenin and p120 occurs frequently in surgical specimens of colorectal and lung cancer, and that phosphorylation of β-catenin correlates well with poor survival of patients after surgery[116,117]. These results suggest that tyrosine phosphorylation of the catenins might be a significant mechanism that modulates their function and, in turn, that of E-cadherin–catenin; this may have important prognostic value.

E-cadherin–catenin expression in cancer and its possible clinical relevance

Immunohistochemical studies of many different types of human carcinomas (including skin, head and neck, lung, breast, thyroid, oesophageal, gastric, pancreatic, hepatocellular, colon, renal, bladder, prostate, endometrial and ovarian carcinomas) have shown that a proportion of these neoplasms have reduced levels of E-cadherin expression in comparison to their related normal tissues. Indeed, E-cadherin loss is most pronounced in those types of carcinoma that have strikingly infiltrative growth patterns associated with little or no intercellular cohesion, such as invasive lobular breast cancer and diffuse-type gastric adenocarcinoma. Therefore, it is not surprising that abnormal expression of the E-cadherin–catenin complex correlates with pathological characteristics of the tumour, such as grade of differentiation, invasiveness, venous permeation, peritoneal seeding, lymph node involvement, liver and bone metastases and tumour stage[16,118–124]. Interestingly, aberrant expression of E-cadherin, α-, β- and γ-catenin, and p120 correlates with clinical variables, such as disease relapse, disease-free survival and overall survival[121,125–131]. Moreover, aberrant expression of E-cadherin and/or the catenins has been shown to be an independent prognostic marker for shorter survival, although its predictive value is usually less strong than that of the standard variables such as tumour grade, tumour stage and lymph node metastases[128,132–136]. Of particular interest is the finding that E-cadherin is an independent predictor of occult lymph node metastasis and micrometastases in nodes classified as N_0 by routine histopathological methods[137]. This is in accordance with studies that show an additive value for E-cadherin–catenin expression in patients with no signs of lymph node or distant metastases (N_0 and M_0)[131,138]. Immunohistochemical detection of E-cadherin and the catenins might be useful not only in predicting disease-free or overall survival but also in identifying patients with clinically negative lymph nodes who are at risk of occult metastases and who may benefit from more extensive lymph node dissection.

A number of studies have failed to show a relationship between E-cadherin–catenin expression and clinicopathological variables[139,140]. Several explanations for this discrepancy can be suggested. The histological type and number of cancers analysed, selection of the tumours (stage, tumour grade), demographics of the study population[141], differences in the surgical approach (extent of lymph node dissection)[118,142], and differences in staining evaluation may individually or in combination be held responsible.

Some studies report that the combination of E-cadherin and one of the catenins is of better prognostic value than evaluation of the individual components[27,143]. It is important to note that alterations in any component may lead to disrupted function of the complex. Since catenins play a critical role in the regulation of cadherin-mediated adhesion, this indicates that E-cadherin immunoreactivity does not always imply the presence of a functionally normal cadherin–catenin complex. Thus, to predict tumour invasion and metastasis in carcinomas, it is useful to investigate not just the expression of E-cadherin but also the expression of the catenins. In addition, these results re-emphasize the importance of understanding the regulatory pathways of cell adhesion in order to interpret correctly the immunohistochemical data on adhesion molecule expression in tumours. Interestingly, the lack of correlation between cadherin and catenin immunoreactivity is also consistent with the promiscuous and yet selective association of catenins not only with E-cadherin, but also with other transmembrane (e.g. EGFR), cytosolic (e.g. APC) and nuclear (Tcf) proteins. Large clinicopathological studies evaluating all members of the adhesion complex within a well defined population, with complete follow-up, are needed to validate the use of E-cadherin and catenins as predictors of tumour cell behaviour.

Alterations in E-cadherin and catenin expression have also been found in preinvasive lesions of the colon (adenoma), oesophagus (Barrett's dysplasia), stomach (gastric dysplasia) and breast (ductal carcinoma *in situ*)[18,19,144,145]. In addition, raised levels of a soluble form of E-cadherin (sE-cadherin; 80 kDa) can be detected in the serum of patients with cancer, possibly induced by tumour-associated proteolytic degradation. In those with bladder cancer a correlation exists between the level of sE-cadherin and grade, stage of the tumour and with tumour recurrence on cystoscopy[146,147]. Furthermore, sE-cadherin may serve as a tumour marker with a rather high sensitivity compared with CA19–9 and carcinoembryonic antigen in patients with gastric cancer[148]. In ovarian carcinoma E-cadherin levels show no correlation with the response to chemotherapy or 5-year survival. Therefore, it may be concluded that determination of preoperative levels of sE-cadherin does not offer useful clinical information for the management of patients with ovarian cancer[149]. Undoubtedly, more evidence from larger studies is needed to address the possible usefulness of sE-cadherin as a disease marker for cancer.

A combination of decreased E-cadherin expression with altered expression of other proteins involved in cancer invasion and metastasis has been described. For example, a combination of decreased E-cadherin expression with upregulation of urokinase-type plasminogen activator (a protease involved in cancer invasion and metastasis) is an independent predictor of prognosis in patients with gastric cancer[150]. Simultaneous reduced expression of E-cadherin and CD44v6 in breast cancer, and low E-cadherin expression in combination with high CD44s in renal cancer, correlates with poorer survival[129,151]. Combination of low E-cadherin immunoreactivity and high type IV collagenase expression is an independent predictor of disease recurrence and overall survival, but not of stage, nodal metastases and histological type, in pancreatic cancer[152]. Finally, Otto *et al.*[118] found that abnormal expression of both E-cadherin and gp78 (the receptor for a tumour-derived autocrine motility factor) in patients with bladder carcinoma results in poor outcome, independent of tumour stage and grade.

Recent studies suggest that modulation of E-cadherin and catenins may be more complex than previously thought. For example, it has been demonstrated that in 40 per cent of adenocarcinomas E-cadherin levels are raised in their intravascular tumour components in comparison to their extravascular compartments[153]. Moreover, expression of E-cadherin or the catenins has been found to be higher in lymph node metastases than in the primary tumour[122,136,145] and, surprisingly, there is a greater tendency for liver metastasis in tumours in which the integrity of E-cadherin-mediated cell adhesion is intact[154]. This strongly suggests that the levels of cadherin–catenins are not necessarily fixed, but in an appropriate microenvironment may be subject to transient manipulation. One explanation may be that entrance of a carcinoma into an intravascular compartment is associated with an upregulation of E-cadherin expression, and that subsequent exit into extravascular tissues is associated with downregulation[155]. Second, upregulation of E-cadherin expression at implantation sites may be necessary for tumour cells to cluster and grow out as metastases. These concepts are supported by *in vitro* data, and the fact that the staining pattern of E-cadherin in human tumours is often heterogeneous and unstable[156,157].

E-cadherin–catenin: a target for anticancer therapy?

Since the function and expression of the E-cadherin–catenin complex is often reduced in cancer cells, it is suggested that restoration of the E-cadherin–catenin will lead to differentiation and anti-invasive properties. Several drugs have been described to alter the expression of E-cadherin, some of which are already used in the treatment of cancer. At least *in vitro*, insulin-like growth factor 1, tamoxifen, taxol, retinoic acid and progestagens have been shown to upregulate the functions of the E-cadherin–catenin complex, including inhibition of invasion[158–162]. The mechanisms by which these drugs induce these changes include upregulation of E-cadherin, α- and β-catenin messenger RNA expression, dephosphorylation of β-catenin, increased stability of the β-catenin protein, and localization of β-catenin at the cell–cell junctions[160,162–164]. A few more drugs may be added to the list of compounds that restore E-cadherin–catenin-dependent cell–cell adhesion; aspirin is probably the most intriguing[165]. Epidemiological, animal model and clinical studies all suggest that non-steroidal anti-inflammatory drugs are potent preventive agents against colon cancer. Mahmoud *et al.*[165] showed that aspirin decreased the rate of tumour formation in MIN mice; these mice have a germline mutation in *APC* which leads to an increase in cytoplasmic β-catenin with subsequent cell signalling. Aspirin produces a decrease in intracellular β-catenin levels, suggesting that modulation of this protein is associated with tumour prevention.

Table 1 E-cadherin–catenin complex: clinical findings and implications

Findings	References
Expression of E-cadherin–catenin correlates with histopathological findings: tumour grade, invasion and wall infiltration, venous permeation, lymph node, liver and bone metastases, tumour stage	26,118–124
Expression of E-cadherin–catenin can predict survival after surgery: overall 5-year survival, 5-year disease-free survival, disease relapse	121,125–131
Expression of E-cadherin can predict occult lymph node metastases/micrometastases	131,137,138
Malignant degeneration: normal epithelium→dysplasia→carcinoma sequence	18,19,144,145
Soluble E-cadherin in sera of patients with cancer could serve as a tumour marker: follow-up of patients, detecting recurrence, response to (adjuvant) therapy?	146–148
Identifying families with hereditary diffuse type of gastric cancer (and lobular breast cancer?)	81,82
Anticancer therapy and cancer prevention: restoring abnormal expression of E-cadherin–catenin by drugs	158–162,165

Conclusions

Inactivation of the E-cadherin–catenin cell–cell adhesion complex is mediated by genetic and epigenetic events that occur in both the early and late stages of carcinogenesis. These molecules may be useful in assessment of the malignant potential of preinvasive lesions and the development of prognostic markers for cancer. *Table 1* summarizes the relevant clinical findings and their possible implications. Apart from epithelial cell–cell adhesion, E-cadherin–catenin is involved to a much wider extent in cancer cell biology. Surprising findings regarding the interaction between APC and β-catenin, and its role in cell signalling, have clearly shown that this complex has a key role in malignant cell transformation. Moreover, elucidation of the mechanisms underlying the changes in E-cadherin and catenin function may lead to the development of novel therapeutic approaches based on biochemical and genetic manipulation.

Acknowledgements

B.P.L.W. was supported by the Netherlands Organization for Scientific Research (NWO).

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Review

Hyperthermic intraperitoneal chemoperfusion in the treatment of locally advanced intra-abdominal cancer

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Background: Surgical treatment of intra-abdominal cancer is often followed by local recurrence. In a subgroup of patients, local recurrence is the sole site of disease, reflecting biologically low-grade malignancy. These patients might, therefore, benefit from local treatment. Recently, debulking surgery followed by hyperthermic chemoperfusion has been proposed in the treatment of locally advanced or recurrent intra-abdominal cancer. This paper reviews the rationale and assesses the currently accepted indications for and results of this novel treatment.

Methods: A systematic web-based literature review was performed. Information was also retrieved from handbooks, congress abstracts and ongoing clinical trials.

Results: A growing body of experimental evidence supports the use of hyperthermia combined with chemotherapy as an adjunct to cytoreductive surgery. Randomized clinical trials are available to support its use in the treatment and prevention of peritoneal carcinomatosis following resection of pathological tumour stage pT_3 or pT_4 gastric cancer; several other phase III trials are ongoing. Numerous phase I and II trials have reported good results for various other indications, with acceptable morbidity and mortality rates. Case mix, limited patient numbers and absence of a standardized technique are, however, a drawback in many of these series.

Conclusion: For a subgroup of patients with peritoneal cancer without distant disease, debulking surgery followed by hyperthermic chemoperfusion may offer a chance of cure or palliation in this otherwise untreatable condition. This novel therapy should, however, be considered experimental until further results from ongoing phase III trials become available.

Paper accepted 7 April 2000

British Journal of Surgery 2000, 87, 1006–1015

Introduction

Despite seemingly curative surgery, 20–30 per cent of patients with gastrointestinal cancer will develop some form of locoregional recurrence as the sole site of cancer recurrence[1,2]. Locoregional recurrent cancer causes significant morbidity and may give rise to secondary metastatic disease, and this group of patients with biologically low-grade disease might, in theory, benefit from local treatment. The same holds true for patients suffering from stage III epithelial ovarian cancer and primary abdominal mesothelioma, diseases that remain confined to the peritoneal surfaces during most of their natural history. Traditionally, locoregional cancer recurrence with widespread peritoneal implantation has been difficult to treat, most patients undergoing palliative procedures or no surgery at all. Although intraperitoneal chemotherapy has been used alone or after surgery, taking advantage of the presence of a peritoneal–plasma barrier, its clinical efficacy is moderate[3]. Recently, cytoreductive surgery followed by hyperthermic intraperitoneal chemoperfusion (HIPEC) has been described for both the treatment and prevention of locoregional cancer spread from various origins, a management plan based on the experimentally noted synergism between hyperthermia and several antineoplastic drugs. The method was first applied clinically in 1980 by Spratt *et al.*[4], who treated a patient with pseudomyxoma peritonei. Since then, a growing number of reports has attracted considerable interest in this therapy. This paper reviews the biological and clinical rationale for HIPEC, and its clinical outcome.

Methods

A literature search was performed using a web-based search engine (Web of Science, Institute for Scientific

Information, Philadelphia, Pennsylvania, USA). With 'hyperthermia or hyperthermic' and 'surgery or surgical' combined in a Boolean search, 646 articles from 1988 to 2000 were retrieved. Relevant papers were selected and checked for references relating to experimental work. Further information was retrieved from handbooks, congress and meeting reports, and communication from researchers active in the field of hyperthermia.

Hyperthermia alone

The tumoricidal properties of hyperthermia have been recognized since ancient times. The observation of spontaneous tumour regression in patients with hyperpyrexia led to the first clinical application of hyperthermia, which consisted of injection of pyrogenic substances in patients suffering from sarcoma[5]. The biophysical effects of hyperthermia are incompletely understood, but probably include membrane protein denaturation, increased neovascular permeability, and perturbation of multimolecular complexes such as the insulin receptor[6–10]. Tumour cell inactivation is time and temperature dependent, and starts at 40–41°C. At temperatures above 43°C exponential inactivation of tumour cells occurs for most rodent cell lines, resembling the effect of ionizing radiation. Human tumour cell lines may be more sensitive to mild hyperthermia (41–42°C) than rodent cell lines[11].

The sensitivity of solid tumours to hyperthermia is probably due to a susceptible microenvironment with low pH, low oxygen tension, low glucose and loss of adaptive vasodilatation in response to heat[12]. The cytotoxic effects of hyperthermia are modified by the phenomenon of thermotolerance and by genetic variability. Thermotolerance describes the observation that cells preheated at mild temperature become resistant to subsequent exposure at the same temperature. This resistance is accompanied by the synthesis of heat-shock proteins, and can be overcome by very prolonged heating or by heating to high temperature[13]. This threshold temperature seems to be higher for human cell lines (44°C), and this has to be taken into account when planning multiple hyperthermia treatments. Heat-resistant clones have been described *in vitro*, and probably exist also in human solid tumours[14]. These subpopulations may, however, be of limited clinical importance.

Hyperthermia with chemotherapy

Both experimentally and clinically, the antitumoral effect of various chemotherapeutic drugs is enhanced by hyperthermia (*Table 1*). This observation is explained by an increase in cell membrane permeability, altered active drug transport and altered cell metabolism[7,19]. Moreover, hyperthermia decreases tumour tissue interstitial fluid pressure, enhancing convection-driven macromolecular drug delivery[20]. A possible disadvantage of the addition of hyperthermia is the induction of multidrug resistance gene (*MDR1*) expression, resulting in the multidrug-resistant phenotype. In the clinical setting, however, this risk has been shown to be minimal[21]. Most clinical experience with hyperthermic chemoperfusion has involved mitomycin C (MMC) or platinum compounds.

Table 1 Pharmacokinetic data on combined chemotherapy and hyperthermia

Reference	Year	Product	AUCp/AUCb
Jacquet *et al.*[15]	1998	Doxorubicin	83
Pestieau *et al.*[16]	1998	Gemcitabine	12
Bartlett *et al.*[17]	1997	Cisplatin	14
Bartlett *et al.*[17]	1997	TNF	4854
Van Goethem *et al.*[18]	1997	Mitomycin C	38

AUC, area under the concentration–time curve in perfusate (AUCp) and blood (AUCb). The AUC is calculated by integrating the concentration curve over time and reflects the total amount of drug present in perfusate or blood. TNF, tumour necrosis factor

MMC is commonly used in the treatment of gastrointestinal cancer, usually in combination with other drugs. *In vitro*, MMC administration to hypoxic tumour cells at 43°C results in a 40-fold increase in cell killing compared with the same concentration at 37°C[22]. Pharmacokinetic analysis of hyperthermic MMC has demonstrated a mean area under the concentration–time curve peritoneal : plasma ratio of 23·5[23]. Furthermore, rapid absorption with resulting high tissue levels of MMC has been reported following intraperitoneal administration[24].

Platinum compounds are widely used in the treatment of epithelial ovarian cancer. *In vitro*, thermal enhancement has been demonstrated for cisplatin, carboplatin, oxaliplatin and lobaplatin[25–27]. The hyperthermia-enhanced activity of cisplatin is explained by the following mechanisms. First, there is increased DNA alkylation, increased turnover to active metabolites and increased activity at low pH (pH less than 6·5)[28,29]. Second, there is an increased production of free oxygen radicals[30]. Finally, cellular cisplatin resistance is reduced by hyperthermia[31,32].

Other drugs that exhibit synergism with hyperthermia in cytotoxicity cell line assays include tumour necrosis factor (TNF) α[33,34], interleukin 1α[35], angiogenesis inhibitors[36], bleomycin[37], doxorubicin[15], carboplatin[37], irinotecan[38], ifosfamide[39], gemcitabine[40] and vinblastine[41].

Table 2 Overview of centres with reported clinical use of hyperthermic intraperitoneal chemoperfusion in the treatment of peritoneal carcinomatosis

Country	No. of centres
USA	7
Canada	1
Brazil	1
Australia	1
Japan	4
China	2
Korea	1
France	2
Belgium	2
Greece	2
UK	1
The Netherlands	1
Switzerland	1
Norway	1
Germany	1
Italy	1
Spain	1
Total	30

Hyperthermia with radiotherapy

Several randomized clinical studies have clearly demonstrated that hyperthermia and radiotherapy act synergistically on tumour tissue[42,43]. This synergism is explained by two phenomena observed in animal experiments. First, hyperthermia is cytotoxic to cells in an environment with low partial pressure of oxygen and pH[44]. Second, hyperthermic treatment at mild temperatures induces reoxygenation of tumour cells, rendering them more sensitive to the effects of radiation therapy (in a rat tumour model)[45]. At higher temperatures (over 43°C) the opposite happens; tumour oxygenation is reduced to a greater extent than with radiation alone, probably owing to heat-induced damage to tumour capillaries[46].

Clinical experience

Hyperthermia alone or as part of multimodal treatment has been applied clinically in cancer therapy for more than two decades. Examples include locoregional treatment of breast cancer recurrence, advanced neck node metastases and superficial melanoma metastases[47–49]. Local heating is usually delivered by microwave, radiofrequency, laser or ultrasound equipment. The delivery of hyperthermia to the peritoneal surfaces by closed perfusion of a heated solution was first described in a clinical situation in 1980[4]. Since that time, a growing number of centres in Europe, the USA and Asia have reported use of the technique (*Table 2*).

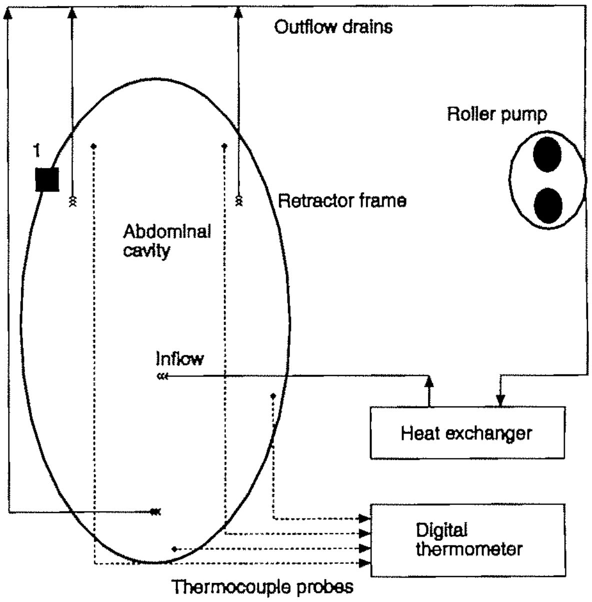

Fig. 1 Schematic representation of the open continuous perfusion technique. Following cytoreduction, the abdominal wall is sutured to a retractor frame fixed on the operating table (1). The frame itself is covered by a plastic sheet with a small slit accommodating the surgeon's hand. A Tenkhoff-type inflow catheter is placed centrally, and multiperforated outflow drains are placed in the left and right subdiaphragmatic space and pelvis. Continuous perfusion is established with a roller pump. Thermocouple probes are placed in the vicinity of the drains; central temperature is monitored with oesophageal or pulmonary artery catheter probes. Cytotoxic drug is added to the perfusate once a temperature of 41·5–44°C is reached. Perfusion is performed over 90 min. Perfusate is continuously distributed throughout the peritoneal cavity manually

Continuous peritoneal perfusion technique

Closed circuit techniques have been described for isolated chemoperfusion of the liver, the kidney, the lung, the limb and the peritoneum[50–54]. The technique of continuous hyperthermic peritoneal perfusion is illustrated schematically in *Fig. 1*. Considerable variation exists in the various descriptions of different technical aspects of HIPEC. Generally, following cytoreduction, one or more Tenkhoff-type inflow catheters and three multiperforated outflow drains are placed, together with temperature probes; chemotherapy is added to the perfusate (usually peritoneal dialysis solution) once a temperature of 41·5–44°C is reached inside the abdomen. Perfusion may be performed following temporary closure of the abdomen, or with an open abdomen technique in which the abdomen is covered with a plastic sheet and drug vapour is evacuated to protect the operating room personnel. Proponents of the latter technique claim better drug distribution by continuous manipulation of the abdominal organs. Closed perfusion, on the other hand, has the advantage of permitting an increase in intra-abdominal pressure that might lead to increased convection-driven drug penetration of macromolecular agents such as TNF-α[20,55,56]. Consensus is lacking about the optimal target temperature. Intra-abdominal temperatures ranging from 41 to 44°C have been described; owing to the demonstrated dose–effect curve of hyperthermia a target temperature of at least 43°C seems advisable.

Intestinal anastomoses are usually constructed after the perfusion in order to facilitate uniform distribution of heat and drug. The influence of intraperitoneally administered chemotherapy and heat on anastomotic healing is a concern. In animal studies, anastomotic healing is impaired by intraperitoneal MMC, but not by 5-fluorouracil, at normal temperature[57,58]. Local hyperthermia in itself has no adverse effects on rat anastomotic healing[59]. When combined with preoperative irradiation, however, hyperthermia has been shown to increase anastomotic complications in a rat model[60].

Toxicity

Extensive cytoreduction followed by HIPEC is associated with considerable rates of morbidity and mortality, and the potential risks of the procedure must be weighed carefully against any potential benefit. In a recent analysis of morbidity and mortality rates following HIPEC with MMC in 60 patients with disseminated colorectal cancer, the postoperative mortality rate was 5 per cent[61]. Complications were noted in 35 per cent of patients, and consisted mainly of anastomotic leak (six), bowel perforation (five) and grade III or IV haematological toxicity (four). In a multivariate analysis, the occurrence of death or complications was associated with the duration of surgery and intra-abdominal temperature, but not with MMC dose. In a recently published randomized trial comparing surgery alone with surgery followed by HIPEC in patients with gastric cancer, postoperative morbidity did not differ between the groups[62]. Postoperative morbidity and death may, therefore, relate mainly to the extent and duration of surgery, and not to the hyperthermic perfusion itself.

Epithelial ovarian cancer

Most patients with ovarian cancer are diagnosed with stage III or IV disease; surgical debulking followed by platinum/paclitaxel-based adjuvant therapy has become the accepted treatment. However, long-term survival is achieved in only 10–20 per cent of patients with stage III disease[63]. Since ovarian epithelial cancer rarely spreads systemically, locoregional chemotherapy might benefit these patients. A large Intergroup trial randomized 654 stage III patients with optimal residual disease (defined as largest nodule 2 cm or less after cytoreduction) to intraperitoneal cisplatin plus intravenous cyclophosphamide or intravenous cisplatin plus intravenous cyclophosphamide[64]. Intraperitoneal therapy was associated with a significantly improved median survival (49 *versus* 41 months) and fewer toxic side-effects. The results of this trial have, however, not substantially altered clinical practice. First, the study was initiated in 1986, before the availability of paclitaxel. Second, somewhat counterintuitively, survival was not dependent on the extent of residual tumour mass. In a subsequent Gynecologic Oncology Group trial, 523 patients were randomized to intravenous cisplatin/paclitaxel or high-dose carboplatin followed by intraperitoneal cisplatin plus intravenous paclitaxel. The recently presented preliminary results demonstrated a significant increase in recurrence-free survival (28 *versus* 22 months), without improvement in overall survival[65]. Paclitaxel administered intraperitoneally has an excellent pharmacokinetic and activity profile in phase I and II trials[66,67]. On the basis of these results, a further Gynecologic Oncology Group trial currently randomizes optimal stage III patients either to intravenous cisplatin/paclitaxel or intravenous paclitaxel plus intraperitoneal cisplatin plus intraperitoneal paclitaxel.

A clear disadvantage of intraperitoneal chemotherapy is the limited penetration into tumour nodules larger than 5 mm[68]. Both in animal experiments and humans, cisplatin has been shown to penetrate much deeper under hyperthermic conditions[27,69]. Several phase I trials of concurrent intraperitoneal platinum compounds and hyperthermic perfusion have, therefore, been initiated. Researchers from the National Cancer Institute of the USA[70] found no toxicity associated with cisplatin perfusion for 90 min at 41–43°C and at a dose of 300 mg/m^2. Further dose escalation was abandoned in favour of the addition of TNF-α to the regimen. The same authors investigated hyperthermic perfusion with high-dose carboplatin in small-volume residual ovarian cancer. Although systemic drug absorption appeared to be unpredictable, carboplatin was safely administered at a dose of 800 mg/m^2. No adverse effects on bowel function, wound healing or anastomotic healing were noted in this small study[71]. Pharmacokinetic data from another phase I trial investigating intraperitoneal cisplatin with hyperthermia revealed a peritoneal : plasma concentration ratio of 15, which is lower than that reported with normothermic intraperitoneal cisplatin[72]. This difference was probably due to increased drug absorption by the addition of hyperthermia. Penetration depth of cisplatin, as measured by DNA adduct formation, was at least 3–5 mm

Table 3 Clinical results of hyperthermic chemoperfusion for treatment or prevention of peritoneal carcinomatosis following resection of gastric cancer

			Survival (%)		
Reference	Year	*n*	Surgery alone	Surgery + HIPEC	*P*
Hamazoe *et al.*[78]	1994	82	52	64	n.s.
Yonemura *et al.*[79]	1995	160	28	50	0·052¶
Kim[80]	1996	52	46	50	n.s.
Sayag-Beaujard *et al.*[81]	1999	42*	—	41‡	—
Fujimoto *et al.*[62]†	1999	141	49§	62§	0·04

*Patients with peritoneal carcinomatosis present at surgery. †Prospective randomized controlled trial. Five-year survival rates are shown unless otherwise indicated; ‡3-year and §8-year rates. ¶A significant survival advantage was noted in a subset of stage III patients. HIPEC, hyperthermic intraperitoneal chemoperfusion; n.s., not significant

and higher than that in buccal cells of the same patients. Intraperitoneal carboplatin with deep hyperthermia generated by external radiofrequency probes has also been studied, but intraperitoneal temperature goals could not be reached because of patient intolerance[73].

In conclusion, chemotherapy can play a small but important role in a subgroup of patients with ovarian cancer who have small-volume residual or recurrent stage III disease. Whether the pharmacodynamic advantage of hyperthermic drug administration will translate into a clinical benefit must be addressed by randomized controlled trials.

Gastric cancer

Locoregional treatment failure is common following resection of gastric cancer, and is explained by both early mural and lymphatic spread, and by peritoneal seeding of exfoliated cells. Lymphatic spread reflects systemic disease, and locoregional treatment alone does not alter long-term survival in this circumstance. This is illustrated by the recent trials comparing standard with extended (D_2) gastrectomy, which did not find a survival advantage associated with more extended lymphadenectomy[74,75]. Macroscopic or microscopic peritoneal spread is present in 40 per cent of patients with stage II and III disease, and is associated with a significant survival disadvantage[76,77].

This observation led several Japanese authors to investigate the usefulness of adjuvant hyperthermic chemoperfusion following pathological tumour stage pT_3/pT_4 gastric cancer resection (*Table 3*). In most of these series, HIPEC was used as a preventive measure with the aim of eradicating microscopic peritoneal implants. A recently published randomized trial investigated the use of prophylactic hyperthermic perfusion with MMC following curative resection of stage II and III gastric cancer[62]. Both the peritoneal recurrence rate and long-term survival were significantly improved in the surgery plus HIPEC group; the postoperative morbidity rate (3 per cent) was not increased. Interestingly, the hepatic recurrence rate was no different between the groups, despite the fact that during HIPEC treatment the liver is exposed to MMC. Although the number of patients treated was small, the results of this trial favour further study of the use of this form of adjuvant treatment.

Colorectal cancer

Next to the liver, the peritoneal surfaces are the most common site for cancer recurrence after 'curative' colorectal cancer resection. Local peritoneal recurrence occurs in as many as 50 per cent of patients with colorectal cancer after resection[2,82]. Peritoneal cancer spread from a colorectal origin has long been regarded as untreatable, and inflicts substantial suffering on the patient. The importance of locoregional therapy is especially relevant in rectal carcinoma, where optimal surgical technique (total mesorectal excision) encompassing possible lateral tumour spread is known to improve local recurrence rates dramatically[83]. In theory, adjuvant intraperitoneal chemotherapy may be beneficial in certain groups of patients with colorectal cancer, provided that maximal surgical cytoreduction is possible. Such groups would be those after resection of advanced (pT_3, pT_4) disease, those having resection of recurrent peritoneal disease, and those with a perforated cancer, positive peritoneal cytology or accidental tumour spillage[84].

The possible role of intraperitoneal chemotherapy in resected high-risk colorectal cancer has been highlighted in a recent randomized trial[85]. In this study, combined intravenous plus normothermic intraperitoneal adjuvant therapy resulted in a 43 per cent reduction in mortality rate in comparison to intravenous chemotherapy alone in resected stage III colon carcinoma. Fujimoto *et al.*[86]

Table 4 Clinical results of hyperthermic chemoperfusion for peritoneal carcinomatosis of colorectal origin

Reference	Year	*n*	Product	Median survival (months)
Yonemura *et al.*[88]	1999	106	Cisplatin + MMC + etoposide	—
Cho *et al.*[89]	1999	56	Cisplatin	—
Bartlett *et al.*[90]	1998	27	Cisplatin + TNF	—
Ma *et al.*[91]	1997	10	Cisplatin	—
Stephens *et al.*[92]	1996	13	Cisplatin	—
Kober *et al.*[93]	1996	25*	MMC or cisplatin	11
Loggie *et al.*[94]	1997	39	MMC	33†
Mansvelt *et al.*[95]	1997	28	MMC	9
Fujimura *et al.*[96]	1999	25	MMC or cisplatin	48
Gilly *et al.*[97]	1999	18	MMC or cisplatin	—
Jähne and Piso[98]	1998	48	Cisplatin	28

*Includes 12 ovarian cancers. †For patients without ascites at surgery. MMC, mitomycin C; TNF, tumour necrosis factor

performed HIPEC following primary resection of rectal cancer in 14 patients. When compared with a control group, the local recurrence rate was significantly improved. Moreover, positive peritoneal cytology was present before surgery in six of the 14 patients treated with HIPEC, but in none of these patients after the procedure. In patients with peritoneal carcinomatosis of colorectal origin, cytoreduction and intraperitoneal normothermic chemotherapy resulted in excellent survival in a large retrospective series[87]. Clinical variables associated with long-term survival were appendiceal origin, grade 1 histology, complete cytoreduction, lymph node-negative disease and volume of cancer present before surgery. Cytoreduction followed by HIPEC in the treatment of peritoneal carcinomatosis of mainly colorectal origin has been reported in numerous phase I and II trials. Most of these studies suffer from methodological flaws, such as inclusion of different primary tumour types, absence of clearly defined endpoints and small patient numbers (*Table 4*). Generally, long-term survival rates of 25–30 per cent are described in groups of patients who undergo complete cytoreduction. Significant prognostic factors include completeness of cytoreduction, lesion size, lesion distribution and tumour histology[99–101]. In an analysis of 18 patients who had second-look surgery following initial debulking with HIPEC, completeness of cytoreduction, both at the initial procedure and at the time of second look, proved to be of prognostic significance[102].

Results from controlled randomized trials are awaited to establish the role of HIPEC in colorectal cancer. A prospective phase III trial comparing intravenous chemotherapy plus cytoreduction plus HIPEC with intravenous therapy alone, in patients with peritoneal carcinomatosis of colorectal origin, was initiated recently at the Netherlands Cancer Institute with promising interim results (F. A. Zoetmulder, personal communication)[103].

Primary peritoneal mesothelioma and sarcoma

Peritoneal mesothelioma is a locally aggressive disease that is relatively unresponsive to systemic chemotherapy. Given its tendency to remain confined to the peritoneal surfaces, intraperitoneal chemotherapy has attracted some interest in the treatment of this disease. Intraperitoneal normothermic cisplatin has resulted in a 59 per cent response rate, but relapse is rapid in most patients[104]. Recently, the results of hyperthermic chemoperfusion with cisplatin for primary peritoneal mesothelioma were reported by researchers at the National Cancer Institute in the USA. Median progression-free survival in 18 patients was 26 months, with a 2-year survival rate of 80 per cent. Ascites disappeared in nine of ten patients after operation[105].

Conclusion

Peritoneal carcinomatosis is generally considered to be an incurable condition. However, a growing body of both experimental and clinical evidence supports the therapeutic and prophylactic use of HIPEC in patients without systemic disease. Level I evidence (from at least one randomized controlled trial) is available on the use of this technique in the prevention and treatment of peritoneal carcinomatosis of gastric origin. Numerous phase I and II trials have been published on primary and metastatic peritoneal carcinomatosis of diverse origin. Owing to the small number of patients and the case mix in these trials, few definitive conclusions may be drawn at this time. However, there is a clear need for well structured randomized trials to establish the role of this promising technique in the treatment of peritoneal carcinomatosis. Many surgeons may not be familiar with the use of hyperthermia as an adjunct to surgery; the authors hope that this article will stimulate their interest.

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Digest

Professor Denis Castaing, Editor of *Annales de Chirurgie*, chooses the best from issues published in 1999. A reciprocal digest written by Professor P. J. Guillou, Associate Editor, is published in the French journal.

Endocrine surgery

Tumours arising from the thyroid follicular cell have proven to be a very useful model for studying the molecular genetics of tumour development. Wynford-Thomas[1] summarizes current knowledge of the principal abnormalities of oncogenes and tumour suppressor genes associated with the major subtypes of thyroid tumour. The pattern that emerges demonstrates well how successive genetic abnormalities drive clonal progression. In addition, comparison of follicular and papillary subtypes provides a fascinating example of how the nature of the underlying genetic abnormality may determine the clinicopathological behaviour of the resulting tumour.

The second paper on thyroidectomy compared double 'high vacuum drains', usually recommended following bilateral thyroidectomy, with a single 'low vacuum drain'. Benoit *et al.*[2] analysed a retrospective study comparing the postoperative outcomes. The clinical features, biochemical profile and histopathology were comparable between group 1 (high vacuum, $n = 77$) and group 2 (low vacuum, $n = 71$). The proportion of total thyroidectomies was significantly greater in group 2 (34 *versus* 51 per cent, $P = 0{\cdot}04$) and this discrepancy was adjusted for in the statistical analysis. There were no wound infections in the two groups. There were no statistically significant differences in the outcome of patients in group 1 *versus* group 2 with respect to incidence of haematoma (zero *versus* 3), duration and volume of drainage (mean(s.d.) 2·1(0·4) *versus* 2·0(0·8) days; 91·6(34·4) *versus* 109·9(41·1) ml) and hospital stay (3·2(0·5) *versus* 3·2(0·9) days). A single 'low vacuum drain' appeared safe and simple for postoperative drainage following bilateral thyroidectomy.

Henry *et al.*[3] propose a new approach to endoscopic parathyroidectomy. Using a 15-mm transverse incision on the anterior border of the sternomastoid muscle, the fascia connecting the lateral portion of the strap muscles and the thyroid lobe to the carotid sheath is divided at the level of the prevertebral fascia. Once enough space has been created, three trocars are inserted: one 12-mm trocar through the incision and two 2·5-mm trocars above and below the first trocar. Carbon dioxide is insufflated at a pressure of 8 mmHg. Unilateral endoscopic parathyroid exploration is then performed with a 10-mm 0° endoscopic camera. Once the adenoma has been identified and, if possible, the ipsilateral parathyroid gland, the three trocars are removed and the adenoma is extracted from the neck after clipping its pedicle directly through the 15-mm incision. Twenty patients with sporadic primary hyperparathyroidism had this operation. The adenoma was localized before operation in 14 patients. Intraoperative quick parathyroid hormone assay was used. Exploration was unilateral in 15 patients. Conversion to open operation was necessary in five patients. In the 50 parathyroid areas explored, 34 glands (68 per cent) were identified by video surgery, 18 of 21 enlarged glands and 16 of 29 normal glands. Mean operating time was 88 (range 40–130) min. Morbidity consisted of two superficial haematomas. With a follow-up ranging from 6 to 15 months, all 20 patients are biochemically cured. This study demonstrated that endoscopic parathyroid exploration can be performed via a lateral incision.

Pancreas

A retrospective review of 30 patients (mean age 26 years), including eight children, with severe duodenopancreatic trauma, treated over 15 years was reported by Jurczak *et al.*[4]. There were 14 patients with duodenal perforation, three with duodenal haematoma, 11 with isolated pancreatic lesions (including five isthmic ruptures), and two with associated duodenal and pancreatic lesions. Injuries were due to road accidents in 60 per cent of cases. Eight patients had multiple injuries and 12 required emergency surgery. Two of the three patients with duodenal haematoma had surgery. All duodenal perforations needed operation, eight as an emergency and six electively. The surgical procedure consisted of simple suture ($n = 3$), suture combined with diversion ($n = 7$) or resection anastomosis ($n = 4$). Five patients with pancreatic contusion had surgery, four because of acute pancreatitis and one for associated lesions. Isthmic ruptures were treated by left pancreatic resection ($n = 3$) or Whipple resection ($n = 1$). The postoperative course was uneventful in seven patients and complicated in five; one patient died from aortic rupture. The authors suggest that duodenal haematoma should be treated conservatively, while duodenal perforations need surgery. The presence of damage to the pancreatic duct frequently justifies pancreatic resection.

To assess the risk of ischaemia in patients undergoing pancreaticoduodenectomy with coeliac trunk occlusion, Berney *et al.*[5] performed a multicentre study, including data from 22 patients (15 men and seven women) with a median age of 66 years. The indication for pancreatic resection was adenocarcinoma of the head of pancreas ($n = 9$), other periampullary tumours ($n = 7$) or chronic pancreatitis

($n = 6$). Trial clamping of the gastroduodenal artery was performed in 16 patients and caused ischaemia in nine, who underwent a revascularization procedure. Of six patients who did not undergo trial clamping, four developed ischaemia during pancreatic resection and unplanned revascularization was necessary. Five (23 per cent) of the 22 patients developed complications, which were fatal in two (mortality rate 9 per cent). The prevalence of coeliac trunk occlusion has been estimated at 2–3 per cent of all patients needing pancreaticoduodenectomy. The authors conclude that the risk of supramesocolic ischaemia is low, but can be minimized by performing trial clamping of the gastroduodenal artery. Revascularization should be performed if trial clamping induces a reduction in blood flow.

Laparoscopic surgery

Non-obstetric abdominopelvic surgery during pregnancy is associated with a considerable rate of maternal and foetal complications. Batallan *et al.*[6] performed a retrospective analysis of nine laparoscopies performed during the second trimester of pregnancy. Laparoscopy realized a diagnostic and therapeutic approach; there were six patients with adnexal disease, two with appendicitis and one had diagnostic laparoscopy. The maternal and obstetric course was favourable in each case. The main theoretical reasons contraindicating laparoscopy after the first trimester of pregnancy are the risk of uterine injury and the fetal risk during creation of the pneumoperitoneum. In the authors' study, laparoscopy during the second trimester of pregnancy was a legitimate diagnostic and therapeutic approach.

Two Nissen fundoplications were performed using a minimally invasive robotic technique by Cadière *et al.*[7]. The Mona robot, placed to the left of the patient, held and activated the surgical tools. The surgeon was located some 3 m from the patient and was seated at a console, unscrubbed. He commanded the three robotic arms by manipulating two handles, while observing a three-dimensional image recreated by a binocular system. Manipulation of the handles was translated into digital information by computer. The information was modified by the computer with downscaling of the amplitude of motion by a factor of 1 : 3 or 1 : 5, eliminating physiological tremor. The computer delivered impulses to the articulated robot arms via a 5-m cable. The operating time was 4·3 and 1·3 h. Blood loss was estimated at 20 and 30 ml. The two patients were discharged on the first postoperative day after a Gastrografin (Schering, Berlin, Germany) swallow to check the position of the wrap and its patency. Surgical robotics may have an increasingly important role in tomorrow's operating theatres.

Oesophagus

Accurate preoperative staging of adenocarcinoma of the oesophagus and cardia is critical for selecting appropriate treatment. Bonavina *et al.*[8] designed a study to assess the role of laparoscopy in detecting intra-abdominal metastatic spread. Some 45 patients with histologically proven adenocarcinoma of the cardia, without any previous treatment, and negative or inconclusive findings at computed tomography (CT) and ultrasonography underwent staging laparoscopy at the same session as the planned surgical resection. The mean operative time of the procedure was 25 (range 15–55) min. Laparoscopy led to a change in the therapeutic approach in five patients: three patients with a peritoneal deposit and one with a liver metastasis undetected at preoperative imaging did not have resection. Conversely, one individual with a liver haemangioma simulating a metastatic mass at CT underwent oesophagogastric resection. Laparoscopy increased the accuracy of detection of metastases when performed as the first step of a planned resection. Unnecessary laparotomy was avoided without increasing the complexity of preoperative evaluation.

The aim of a study by Bilosi *et al.*[9] was to review morbidity and mortality rates associated with 42 colon substitutions after resection for oesophageal cancer. Colon substitution was the intervention of first choice in six patients. In the others the stomach was useless, because of previous gastric surgery ($n = 14$), gastric involvement by the tumour ($n = 21$) or a technical problem ($n = 1$). Patients were reviewed in two groups: from 1969 to 1983 (group A, $n = 22$), and from 1983 to 1997 (group B, $n = 20$). The total morbidity rate was 57 per cent, 77 per cent in group A and 35 per cent in group B ($P < 0{\cdot}05$). Cervical and colocolic leakages were the most common complications. The total mortality rate was 14 per cent, 22 per cent in group A and 5 per cent in group B ($P < 0{\cdot}01$). In group A, three patients died from anastomotic leak (intrathoracic or intra-abdominal) and two from medical complications. In group B, one patient died from unexplained sepsis. The authors concluded that their latest results of colonic substitution were comparable to those of gastroplasty for cancer or coloplasty for benign disease.

Colon

Loop ileostomy ensures faecal diversion to protect an anastomosis or prevent colorectal or anoperineal damage. The aim of a retrospective study from Petit *et al.*[10] was to evaluate loop ileostomy in emergency and planned colorectal surgery. Some 145 loop ileostomies were performed in 139 patients, 77 men and 62 women with a mean age of 49 (range 15–82) years. The aetiology was a rectal tumour (cancer or large villous tumour $n = 47$), inflammatory bowel disease ($n = 47$; 37 cases of ulcerative colitis and ten of Crohn's disease), familial adenomatous polyposis ($n = 13$) and other diseases ($n = 32$). In 116 patients (80 per cent), loop ileostomy protected ileoanal anastomoses ($n = 46$), coloanal anastomoses ($n = 45$; 26 with a colonic pouch), ileorectal anastomoses ($n = 11$) and other anastomoses ($n = 15$). Twenty-nine loop ileostomies (20 per cent) defunctioned anoperineal lesions ($n = 8$), anastomotic leaks ($n = 4$) or distal bowel without intestinal resection ($n = 17$). The seven deaths were not stoma related. Some 91 per cent of loop ileostomies were closed after a mean diversion interval of 3·6 months. Loop ileostomy closure was performed by a parastomal procedure ($n = 128$) or laparotomy ($n = 4$). Morbidity during loop ileostomy diversion was observed in 24 patients (17 per cent). Twelve (8 per cent) had reoperation, six (4 per cent) for small bowel obstruction, five (3 per cent) for stoma revision and one for prolapse. Two patients had peristomal skin excoriation and five required readmission for dehydratation owing to a high ileostomy output. Morbidity after ileostomy closure was observed in 12 patients (9 per cent); five had reoperation for anastomotic leakage ($n = 4$) or small bowel obstruction ($n = 1$). Low morbidity and defunctioning efficiency confirmed the indications for loop ileostomy in planned or emergency colorectal surgery.

D. Castaing
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Annales de Chirurgie

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Original article

Severity of acute pancreatitis: a multivariate analysis of oxidative stress markers and modified Glasgow criteria

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Background: It is unknown whether measurement of markers of oxidative stress can improve the prediction of severity of acute pancreatitis.

Methods: Consecutive patients admitted with a diagnosis of acute pancreatitis were divided into mild ($n = 62$) and severe ($n = 23$) groups based on the Atlanta classification. Plasma oxidative stress markers were measured within 24 h of admission and included ascorbic acid (endogenous antioxidant), protein carbonyl (a marker of protein oxidation), thiobarbituric acid reactive substances (a marker of lipid peroxidation) and myeloperoxidase (a neutrophil enzyme that produces oxidants). Canonical correlation analysis was used to describe the relationship between these markers and the modified Glasgow criteria. Canonical variate analysis was used to define the best variables that could discriminate mild and severe pancreatitis.

Results: There was a significant correlation between markers of oxidative stress and the modified Glasgow criteria (first canonical correlation 0·69, $P < 0·0001$, Wilk's lambda test). Blood urea, serum albumin and white cell count were the best variables that discriminated mild and severe acute pancreatitis, and all were better than the oxidative stress markers.

Conclusion: The markers of oxidative stress were highly correlated with the severity of pancreatitis. They are unlikely to be better than the modified Glasgow criteria in predicting it.

Presented to a meeting of the Royal Australasian College of Surgeons Annual Scientific Congress in Auckland 1999, and published in abstract form as *Aust NZ Surg J* 1999; 69(Suppl): A54
Paper accepted 2 February 2000
British Journal of Surgery 2000, **87**, 1019–1023

Introduction

The optimal management of acute pancreatitis requires an accurate prediction of the disease severity and expected course. This allows patients with severe pancreatitis to be more intensively monitored and treated. In most cases acute pancreatitis has a mild course. About a quarter of cases progress to severe pancreatitis[1] which is still associated with a high mortality rate (up to 40 per cent) despite advances in management. Many methods have been devised to predict the severity of pancreatitis, including multiple clinical and biochemical variables (e.g. Ranson[2] and Glasgow[3] criteria), single variables (e.g. trypsinogen activation peptide and C-reactive protein), radiological (e.g. contrast-enhanced computed tomography) and more invasive (e.g. peritoneal aspiration) methods[4–6].

Recent research has indicated that oxidative stress occurs early in acute pancreatitis, that it is related to the severity of pancreatitis and that it may have an important role in the pathogenesis of pancreatitis[1,7]. Oxidative stress occurs when oxygen-derived free radicals overwhelm endogenous oxidative defences, causing damage to cellular constituents. Ascorbic acid is one of the most important endogenous antioxidants in the body[8]. Other markers of oxidative stress include plasma protein carbonyl, a marker of protein oxidation[9,10]; thiobarbituric acid reactive substances (TBARS), a marker of lipid peroxidation[11]; and myeloperoxidase (MPO), a neutrophil enzyme that produces oxidants[12]. It is not known whether incorporating markers of oxidative stress can improve the ability to accurately predict the severity of acute pancreatitis.

This study was designed to define the relationship between oxidative stress markers (OSM) and the modified Glasgow criteria (MGC) in acute pancreatitis and to compare them as predictors of severity using multivariate analyses.

Patients and methods

Consecutive patients admitted with a diagnosis of acute pancreatitis were recruited over an 18-month period. The diagnosis of acute pancreatitis was based on a serum amylase level above 1000 units/l (Phadebas; Pharmacia Diagnostics, Uppsala, Sweden) (upper limit of normal 300 units/l) in association with typical abdominal pain. Written informed consent was obtained and the study was approved by the Northern Regional Health Authority Ethics Committee. The details of these patients have been published before in another context[1].

The patients were divided into groups with mild and severe pancreatitis, based on their actual clinical outcome, in accordance with the Atlanta classification[13]. The predicted severity of patients on admission was determined by the MGC[3].

Assays

Peripheral blood samples were taken from the fasting patients on recruitment. The blood was transported in heparinized tubes for immediate centrifugation and the plasma was stored at – 80°C for subsequent analysis.

MPO was measured as a marker of neutrophil activation using tetramethylbenzidine[14]. Plasma (0·1 ml) was mixed with 0·9 ml 100 mmol phosphate buffer containing 0·025 per cent cetrimide and added to 0·1 ml CM-Sepharose CL-6B beads (Pharmacia). The beads were washed and the adsorbed MPO was then eluted with sodium sulphate 0·5 mol/l. This step was necessary to separate components of plasma (probably ceruloplasmin) that interfered with the assay.

Protein carbonyls were measured as a marker of protein oxidation using an enzyme-linked immunosorbent assay (ELISA)[9]. The plasma samples were reacted with dinitrophenylhydrazine (DNP), adsorbed to ELISA wells, then reacted with a biotinylated antibody raised against protein-conjugated DNP (Molecular Probes, Eugene, Oregon, USA) followed by streptavidin–biotinylated horseradish peroxidase (Amersham International, Amersham, UK) for quantification.

Ascorbic acid was measured as a marker of endogenous antioxidant activity by high-pressure liquid chromatography (HPLC) (Walters 600E; Millipore, Medford, Massachusetts, USA) using a C18 reverse phase column (5-μm octadecyl silane, 220 × 4·6 mm) with an electrochemical detector (Phillips Pye Unicam PU4022; Unicam, Cambridge, UK)[15]. This assay only measures reduced ascorbate. The smallest peaks measured were at least twice the average background fluctuation, and varied between 0·3 and 1·0 μmol/l from day to day. Concentrations below 1 μmol/l were classified as not detectable. Duplicates measured in the same run varied by 5 ± 4 per cent ($n = 14$). The intra-assay coefficient of variation for a plasma sample containing 60 μmol ascorbate was 3·9 per cent.

TBARS were measured as a marker of lipid oxidation by HPLC with fluorescence detection[16]. This method measures primarily protein-bound malondialdehyde.

Statistical analysis

The statistical analyses were performed using the SAS program (version 6.12 for PC; SAS Institute, Cary, North Carolina, USA). The assumption of multivariate normality was tested, and the data were transformed and tested until the best normal distribution was reached using the Shapero–Wilk test for normality. The transformed data were then used for subsequent analyses. Student t test was used for univariate analysis to compare the transformed data of the studied variables of the two groups. $P < 0·05$ was accepted as significant.

When calculating a multiple correlation between multiple dependent and independent variables, it is possible to perform separate regressions for each dependent variable. However, this would not allow an exploration of all the variation in the data. A method that takes all the information into account, thus giving a better understanding of all the relationships, is canonical correlation which was used in this study to describe the relationship between the OSM and MGC. The first canonical variate of this analysis is defined as a linear combination of the MGC with the weighting selected to maximize the correlation with the canonical variate of OSM[17,18].

Canonical variate analysis was used to define the best variables to discriminate between the mild and severe pancreatitis groups[17]. The first canonical variate of this analysis is defined as a linear combination of MGC and OSM with weighting calculated to produce the maximum discrimination between mild and severe pancreatitis as defined by actual clinical outcome.

Results

There were 85 patients (44 men and 41 women, of median age 56 (range 16–96) years) recruited into the study, of whom 62 had mild and 23 severe pancreatitis. The demographic details have been published previously[1].

The methods of data transformation are shown in *Table 1*. The Shapero–Wilk test for normality could not reject the normal assumption for age, albumin and TBARS, and transformation was not needed for them. Arterial oxygen tension had two separate populations that could not be transformed to normal distribution because of missing

Table 1 Mean and back-transformed mean of the transformed modified Glasgow criteria and the oxidative stress markers

		Mild pancreatitis		Severe pancreatitis		
Variable	Transformation	Mean	Back-transformed mean	Mean	Back-transformed mean	P*
Albumin	None	34·09(3·46)		28·65(4·16)		0
Urea	Log	1·69(0·43)	5·42	2·24(0·45)	9·39	0
White cell count	Log	2·53(0·34)	12 553	2·95(0·31)	19 105	0
Glucose	X^{-1}	0·13(0·04)	7·69	0·095(0·03)	10·52	0·0001
Ascorbic acid	$X^{0·6}$	4·92(2·3)	14·3	2·83(2·09)	5·66	0·0003
Calcium	X^{4}	18·25(4·8)	2·07	15·17(5·48)	1·97	0·016
Protein carbonyl	$X^{-0·2}$	1·79(0·29)	0·05	1·51(0·52)	0·13	0·018
Lactate dehydrogenase	Log	5·49(0·62)	242·25	5·87(0·81)	354·24	0·03
Age	None	53(18·35)		60·34(17·6)		0·1
Myeloperoxidase	$X^{0·5}$	1·61(0·38)	2·59	1·82(0·53)	3·31	0·11
TBARS	None	1·70(0·54)		1·74(0·52)		0·8

Values are mean(s.d.). TBARS, thiobarbituric acid reactive substances. *Student *t* test

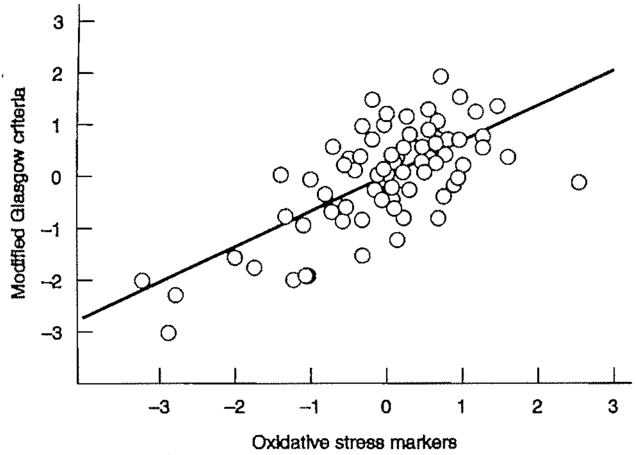

Fig. 1 Correlation between the first canonical variate of the modified Glasgow criteria and the first canonical variate of oxidative stress markers (first canonical correlation 0·69, $P < 0·0001$, Wilk's lambda test)

values (23 of 85). Similar results were obtained when data analysis was performed with and without arterial oxygen tension. The data presented in the manuscript are those with arterial oxygen tension excluded. *Table 1* shows the results of the comparison between the transformed variables of the two groups. The greatest significant difference was for urea, white cell count and albumin. There was no statistical difference for age, MPO or TBARS.

Canonical correlation analysis

There was a very significant correlation between the first canonical variate of MGC and the first canonical variate of OSM (0·69, $P < 0·0001$, Wilk's lambda test) (*Fig. 1*) which was greater than any of the correlations between individual variables of the MGC and OSM.

The first canonical variate for MGC represents patients with a high albumin level, low white cell count and low urea concentration and had a strong positive correlation with the transformed data of protein carbonyl and ascorbic acid. The first canonical variate for the OSM represents patients with a low protein carbonyl (high transformed protein carbonyl) and high ascorbic acid level, and had a strong positive correlation with albumin and a poor negative correlation with white cell count (*Table 2*).

Canonical variate analysis

The first canonical variate resulted in a significant discrimination between patients with mild and severe pancreatitis ($P < 0·0001$, Wilk's lambda test). The variables are listed in order of their ability to discriminate between the two patient groups (*Table 3*). Protein carbonyl and ascorbic acid were the best OSM for predicting the actual severity of pancreatitis, but these were not as strong in predicting clinical outcome as albumin, urea, white cell count and glucose.

Discussion

This study has shown that OSM are highly correlated with the severity of pancreatitis, but are not as useful as the MGC in predicting severity.

The most commonly used methods for predicting the severity of acute pancreatitis, the MGC and Ranson criteria, were developed before it was recognized that levels of OSM

Table 2 Correlations between the first canonical variate of modified Glasgow criteria and oxidative stress markers and each of the studied variables

	First canonical variate of the MGC	First canonical variate of the OSM
Age	−0·21	−0·14
Albumin	0·90	0·62
Calcium	0·24	0·17
Glucose	0·36	0·24
Lactate dehydrogenase	−0·22	−0·15
Urea	−0·50	−0·35
White cell count	−0·59	−0·41
Ascorbic acid	0·45	0·66
Myeloperoxidase	−0·22	−0·32
Protein carbonyl	0·57	0·83
TBARS	0·05	0·07

MGC, modified Glasgow criteria; OSM, oxidative stress markers; TBARS, thiobarbituric acid reactive substances

Table 3 Studied variables in order of their ability to predict severity of pancreatitis

Variable	Canonical variate	Markers/criteria
Albumin	0·57	MGC
Urea	−0·54	MGC
White cell count	−0·48	MGC
Glucose	0·42	MGC
Ascorbic acid	0·35	OSM
Protein carbonyl	0·28	OSM
Lactate dehydrogenase	−0·23	MGC
Myeloperoxidase	−0·21	OSM
Calcium	0·19	MGC
Age	−0·12	MGC
TBARS	−0·05	OSM

MGC, modified Glasgow criteria; OSM, oxidative stress markers; TBARS, thiobarbituric acid reactive substances

were raised early in the course of the disease[7,19]. It is not known whether inclusion of OSM can improve the prediction of the severity of acute pancreatitis.

The four markers of oxidative stress used in this study represent different aspects of oxidative stress. MPO is a marker of neutrophil activation that produces oxidants by catalysing hypochlorous acid[12]. The level of ascorbic acid, a potent endogenous aqueous antioxidant, is significantly decreased in the plasma of patients with acute pancreatitis and is related to severity[1,8]. Protein carbonyl is a relatively specific marker of oxidative damage to proteins[10]. It is increased in the tissues and plasma in inflammation and ischaemia–reperfusion injury[20–22], and increases proteolysis which affects the function of proteins[21,23]. Lipid peroxidation, which is indicated by an increased concentration of malondialdehyde in tissues or tissue fluids[24], can be measured as TBARS[20].

The MGC, rather than the Ranson criteria, were used in this study because they can be calculated during the first 24 h after admission and because they are probably more relevant to this study population. In Ranson's series of patients there was a marked predominance of alcohol-associated pancreatitis[2], compared with only 9 per cent of patients in this study. The MGC did not accurately predict two patients with severe pancreatitis and eight with mild pancreatitis in this study (sensitivity 91 per cent, specificity 64 per cent, positive predictive value 72 per cent, negative predictive value 96 per cent). Although the MGC err on the side of overestimating the severity of pancreatitis, the low positive predictive value clearly indicates that there is room for improvement in the accurate prediction of the severity of pancreatitis in individual patients.

Multivariate analysis has the ability to correlate one group of variables with another group of variables. The correlation between the first canonical variate of MGC and of OSM was significant. The first canonical variate for MGC represented patients with high levels of albumin and low levels of urea and white cell count or those with mild pancreatitis. The first canonical variate for OSM was attributed to high levels of ascorbic acid and low levels of protein carbonyl, also a reflection of mild pancreatitis.

Canonical variate analysis showed that the most important variables in discriminating between mild and severe pancreatitis were serum albumin and blood urea. Interestingly, when data were analysed to include arterial oxygen tension, it was not a strong predictor of outcome even though it is a direct marker of the respiratory function, and respiratory failure is a hallmark of severe pancreatitis. This is supported by a recent prospective clinical study which showed that, although respiratory failure was the most common organ system to fail, it carried the lowest mortality risk[25].

Ascorbic acid had a greater predictive ability than protein carbonyl in this study. Interestingly, protein carbonyl was the only one of the OSM with a significant simple correlation with Acute Physiology And Chronic Health Evaluation II score within 24 h of admission ($r_S = 0{\cdot}41$, $P < 0{\cdot}00008$).

Lipid peroxidation was not a good predictor of severity of pancreatitis in this study. This is supported by the finding that the TBARS assay provided little evidence of oxidative injury in patients with trauma and sepsis[20]. In contrast, Goode *et al.*[26] showed that lipid peroxidation as measured by TBARS was significantly increased in patients with septic shock. The method of analysis (HPLC) used in the present study improves specificity by separating malondialdehyde–TBAR adduct. This may account for the difference in the results[20].

Oxidative stress is a feature within the first 24 h of the onset of acute pancreatitis[1,7,27]. This study compared OSM and the MGC as predictors of the severity of acute pancreatitis. While the OSM were highly correlated with the severity, they were no better than the MGC in predicting it.

Acknowledgements

This work was supported by the Auckland Medical Research Foundation, the Maurice & Phyllis Paykel Trust and the Health Research Council of New Zealand. F. Abu-Zidan was supported by an Auckland Medical Research Foundation Fellowship. Dr Bonham was supported by a Ruth Spencer Medical Research Fellowship. The authors are grateful for the guidance of Dr Denny Meyer, Senior Lecturer in Statistics at Massey University, Auckland for help with the analyses. OSM were measured by Professor Christine Winterbourn, Free Radical Research Unit, Department of Pathology, Christchurch School of Medicine, Christchurch.

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Original article

In vivo evaluation of an implantable portal pump system for augmenting liver perfusion

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Background: Increasing portal inflow in cirrhosis using a mechanical pump reduces portal venous pressure and improves liver function. A pump has been developed for portal vein implantation in human cirrhosis. This study describes the initial *in vivo* evaluation in a porcine model.

Methods: Five Large White pigs underwent laparotomy and exposure of the liver. Flow in the hepatic artery, portal vein and hepatic microcirculation was monitored continuously. Hepatic tissue oxygenation was measured by near-infrared spectroscopy. After baseline measurements the pump was inserted into the portal vein. Pump flow rate was then increased stepwise to 50 per cent over the baseline value for a period of 2 h. The pump was then stopped for 20 min and left *in situ* while continuing to collect systemic and hepatic haemodynamic data. The animal was killed and biopsies for histological examination were taken from the liver, small intestine and spleen.

Results: The baseline total hepatic blood flow was 626(39) ml/min; the hepatic artery supplied 18·4(2·1) per cent and the portal vein 81·6(2·1) per cent. The pump was inserted successfully in all animals without surgical complications. During surgical insertion of the pump, the temporary portal vein occlusion resulted in a significant rise in hepatic artery blood flow (22(3) per cent; $P < 0{\cdot}01$ *versus* baseline). Portal vein flow was augmented by pumping; there was a significant correlation between the pump motor speed and portal vein flow ($P < 0{\cdot}0001$). This inflow correlated directly with flow in the hepatic microcirculation and hepatic tissue oxygenation ($P < 0{\cdot}001$). The pump ran satisfactorily throughout the study. Histological examination revealed no evidence of structural damage to the liver or ischaemic changes in the small intestine or spleen.

Conclusion: It is technically possible and safe to insert an implantable pump in the portal vein. Portal venous blood flow can be increased up to 50 per cent with a resultant increase in flow in the hepatic microcirculation and hepatic oxygenation and without adverse effects on either hepatic or systemic haemodynamics.

Paper accepted 24 January 2000

British Journal of Surgery 2000, 87, 1024–1029

Introduction

In 1991 a new concept for reduction of portal venous pressure in portal hypertension was introduced by mechanically pumping portal blood[1]. Subsequently, *in vitro* experiments on both animal and human cirrhotic livers suggested that enhancing the portal venous inflow mechanically twofold and fourfold would reduce portal venous pressure, intrahepatic vascular resistance and improve liver function, without damaging effects on hepatic morphology[2–4]. Although these studies on bench-perfused cirrhotic livers may not reflect *in vivo* findings, similar results have recently been demonstrated in animal models with portal hypertension and extensive hepatic fibrosis[5,6]. Short-term mechanical pumping of portal inflow to the human cirrhotic liver *in vivo* in patients undergoing orthotopic liver transplantation demonstrated similar results[7]. Following these promising results an implantable pump has been designed and developed for human use. The pump's performance, hydraulics and its induction of haemolysis have been measured *in vitro* in a flow circuit[8]. This study assessed the feasibility of surgical insertion of an implantable pump into the portal vein in a normal porcine model and the effects of short-term enhancement of portal inflow.

Methods

Implantable pump

The pump has been designed and developed for human implantation. The technical aspects of the pump have been described previously[8]. The pump is electrically operated and uses an impeller to force blood through its central lumen. It has been designed to be fixed to the vessel wall to prevent backflow. The impeller allows flow through the pump even when the pump is not being driven. The pump speed can be increased remotely, resulting in a progressively increased portal flow rate.

Anaesthesia and monitoring

The study was conducted under a licence granted by the Home Office in accordance with the Animals (Scientific Procedures) Act 1986. Large White pigs ($n = 5$; mean(s.d.) weight 24(2) kg) were used. Following an overnight fast, the animals were premedicated with intramuscular azaperone (Stresnil; Janssen Pharmaceutical, Oxford, UK) 0·1 ml/kg. After induction of anaesthesia using intravenous ketamine hydrochloride (Ketaset; Willows Francis Veterinary, Crawley, UK) 5 mg/kg, the animals were intubated and mechanically ventilated. Anaesthesia was maintained with halothane (May and Baker, Dageham, UK), nitrous oxide and oxygen via a standard anaesthetic circuit. The animal's temperature was maintained at 36–38°C by means of an electronic heating mat. A pulse oximeter probe (Ohmeda Biox 3740 pulse oximeter; Ohmeda, Louisville, Colorado, USA) was used for continuous monitoring of arterial oxygen saturation and heart rate. A polyethylene catheter was placed into the external jugular vein for administration of fluids and into the carotid artery for monitoring of arterial blood pressure. Normal saline was infused via the venous access during the experiment at an hourly rate of 10 ml/kg to compensate for operative fluid loss.

Assessment of hepatic blood flow and flow in the hepatic microcirculation

For continuous measurement of portal vein and hepatic artery blood flow, a dual Transonic Medical Flowmeter system (HT207; Transonic Medical, Ithaca, NY, USA) was used with perivascular flow probes 4 and 8 mm in diameter for the hepatic artery and portal vein respectively[9].

Flow in the hepatic microcirculation was measured by laser Doppler flowmetry (LDF) (DRT4; Moor Instruments, Axminster, UK), which has previously been shown to be reliable and reproducible[10,11].

Hepatic tissue oxygenation

This was measured by near-infrared spectroscopy (NIRS) as described previously[12–15]. The NIRS instrument used in this study (NIRO-500; Hamamatsu Photonics KK, Hamamatsu, Japan) contained a computer programme developed for use on the liver which continuously recorded concentration changes of hepatic oxyhaemoglobin, deoxyhaemoglobin and cytochrome oxidase in micromoles per litre of tissue (μmol/l)[13,14]. A pair of NIRS probes was placed, with a 25-mm separation, on the surface of the right lobe of the liver for continuous monitoring of hepatic tissue oxygenation.

Experimental procedures

Laparotomy was performed through a transverse subcostal incision. The ligamentous attachments of the liver to the diaphragm and the abdominal wall were divided and the liver was exposed. The porta hepatis was exposed and the portal vein and hepatic artery were identified and carefully dissected.

After a period of stabilization (10 min), baseline hepatic and systemic haemodynamic measurements were taken and the liver was biopsied (*Table 1*). The proximal and distal portions of the portal vein were then clamped. A 1-cm portal venotomy was performed and the portal pump was introduced into the portal vein (*Fig. 1*). In two animals 2000 units heparin were injected intravenously before insertion of the pump. The venotomy was then immediately closed with a 5/0 polydioxanone suture and the pump was fixed to the portal vein wall by tying a no. 1 silk ligature around the portal vein. Clamps were removed and immediately the pump was switched on to set a flow level approximately equal to the baseline value before pump insertion. After a 30-min period of baseline portal inflow, the pump speed was gradually increased until the portal venous inflow was 50 per cent over the baseline. The portal inflow was then set at this value for a period of 2 h. At the end of the enhanced portal inflow, multiple biopsies were taken from liver, spleen and small intestine to assess the structural and vascular effects of mechanically increased portal inflow on these organs. All biopsies were fixed with 10 per cent formalin solution and later with haemotoxylin and eosin. All examinations were carried out by an experienced histopathologist using

Table 1 Systemic and hepatic haemodynamics and microcirculation before and after insertion of the portal pump

		After insertion			
Haemodynamic data	Baseline before insertion	Baseline PVF	+25%*	+50%*	Pump off
Hepatic data					
Portal venous flow (ml/min)	511(57)	548(24)	612(37)	674(79)	284(18)
Hepatic arterial flow (ml/min)	115(13)	104(10)	102(12)	98(9)	99(8)
Deoxyhaemoglobin (μmol/l)	10·0(3·1)	−7·0(4·4)†	−28·3(11·6)†	−38·2(15·4)†	−17·4(5·2)†
Oxyhaemoglobin (μmol/l)	25·7(5·6)	34·3(6·7)	39·0(12·3)†	48·2(18·4)†	8·0(4·2)†
Cytochrome oxidase (μmol/l)	0·0(0·3)	0·0(0·2)	1·6(0·3)	1·2(1·8)	−0·5(0·1)
Hepatic microcirculation (flux units)	200(10)	175(11)†	200(18)	254(15)†	150(6)†
Liver temperature (°C)	37(1)	37(1)	37(1)	37(1)	37(1)
Systemic data					
Mean arterial pressure (mmHg)	63(3)	62(2)	65(1)	63(2)	62(4)
Body temperature (°C)	38(1)	38(2)	38(1)	37(1)	38(1)
Heart rate (beats per min)	116(13)	120(17)	119(18)	121(12)	130(12)
Oxygen saturation (%)	100(0)	100(0)	99(1)	100(0)	99(1)
Arterial blood pH	7·23(0·02)	7·25(0·01)	7·24(0·01)	7·23(0·02)	7·24(0·03)

Values are mean(s.d.). *Pumping up to 25 and 50 per cent over the baseline portal venous inflow value. PVF, portal venous flow. †$P < 0{\cdot}05$ *versus* baseline (Student's *t* test)

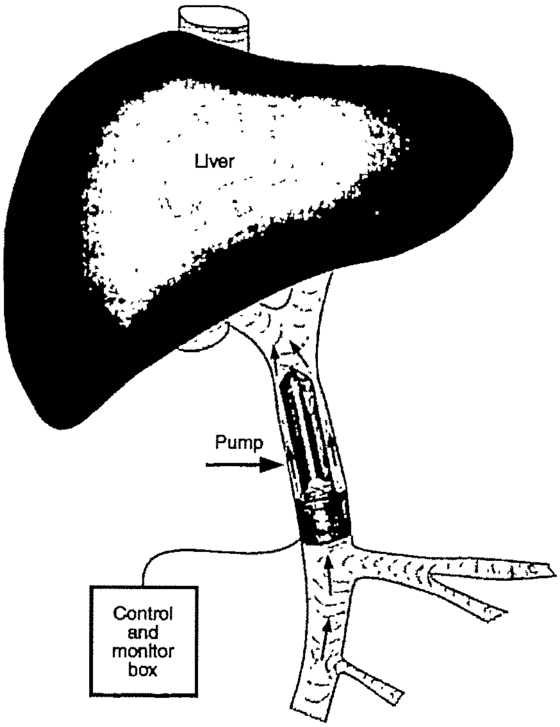

Fig. 1 Implantable portable pump system *in situ*

light microscopy. Finally, the pump was switched off for 20 min to simulate pump failure due to mechanical or electronic complications.

Data collection and statistical analysis

The output from Transonic Medical Flowmeter system, LDF and pulse oximeter together with NIRS data were fed into a laptop personal computer. The systemic haemodynamic data were fed into a commercially available analogue to digital data acquisition recording system (MacLab; AD Instruments Ltd, Hastings, UK). During the process of enhanced portal inflow, hepatic and systemic haemodynamic data were monitored continuously at a rate of 1 Hz. All haemodynamic data were averaged over 2 min. The values are expressed as mean(s.d.). For statistical analysis Student's *t* test was used to compare values obtained before and after portal pumping. $P < 0{\cdot}05$ was considered statistically significant. The relationship between the hepatic haemodynamics and pump flow rate was tested using linear regression.

Results

Surgical technique

Insertion of the pump into the portal vein was achieved in all animals, although meticulous surgical dissection was required around the portal triad. There were no operative deaths or complications. The portal vein in pigs measured a mean(s.d.) of 9(1) mm in diameter and 30(2) mm in length. The operative blood loss was 13(3) ml, and occurred from the venotomy site. The mean time for clamping the portal vein to allow pump insertion was less than 8 min. In the first three pigs no intravenous heparin was given before insertion of the portal pump, and thrombus was noted around the pump impeller at post-mortem examination. However, the pump performance was not affected by thrombus during the period of *in vivo* pumping. Hence, in the final two pigs, heparin 2000 units was given intravenously 5 min before the venotomy, which prevented the formation of thrombus around the portal pump. Fixation of the pump to the portal vein was essential to prevent backflow between the pump and portal vein. This was readily achieved by a ligature around the portal vein. The fixation was satisfactory during the short period of portal pumping studied.

Haemodynamic data

During surgical insertion of the pump, the temporary PV occlusion resulted in a significant rise in HA blood flow (22(3) per cent; $P<0{\cdot}01$ *versus* baseline). Increasing the portal venous inflow by 25 or 50 per cent over baseline resulted in no significant change in systemic haemodynamics (*Table 1*). The blood pH was also stable during the period of augmentation of the portal inflow (*Table 1*).

At baseline, portal venous inflow was 511(57) ml/min, hepatic arterial flow was 115(13) ml/min and portal venous pressure 8(3) mmHg. Increasing the portal inflow by 50 per cent over the baseline flow was achieved successfully in all animals, although occasional collapses of the portal vein were noticed on the mesenteric side of the pump if the flow rate was increased rapidly with augmented PV flow by pumping, there was a significant correlation between the pump motor speed and PV flow ($r=0{\cdot}98$; $P<0{\cdot}0001$). The increase in portal blood flow was immediately reflected by enhanced flow in the hepatic microcirculation and hepatic tissue oxygenation. The increase in hepatic tissue oxygenation and hepatic microcirculatory flow correlated with enhanced portal venous blood flow ($r=0{\cdot}93$ and $r=0{\cdot}96$ respectively, $P<0{\cdot}001$). When the pump was stopped there was an immediate drop in the portal venous inflow (48(6) per cent) together with a corresponding decrease in hepatic microcirculatory flow and hepatic tissue oxygenation (*Table 1*). A typical example is shown in *Fig. 2*. The changes in hepatic intracellular oxygenation were not significant despite augmented portal flow (*Table 1*).

Histological examination

Following the enhanced portal inflow, macroscopic and microscopic examination of biopsies taken from the liver, small bowel and spleen showed no evidence of ischaemic change or morphological damage. No intrahepatic thrombosis was seen.

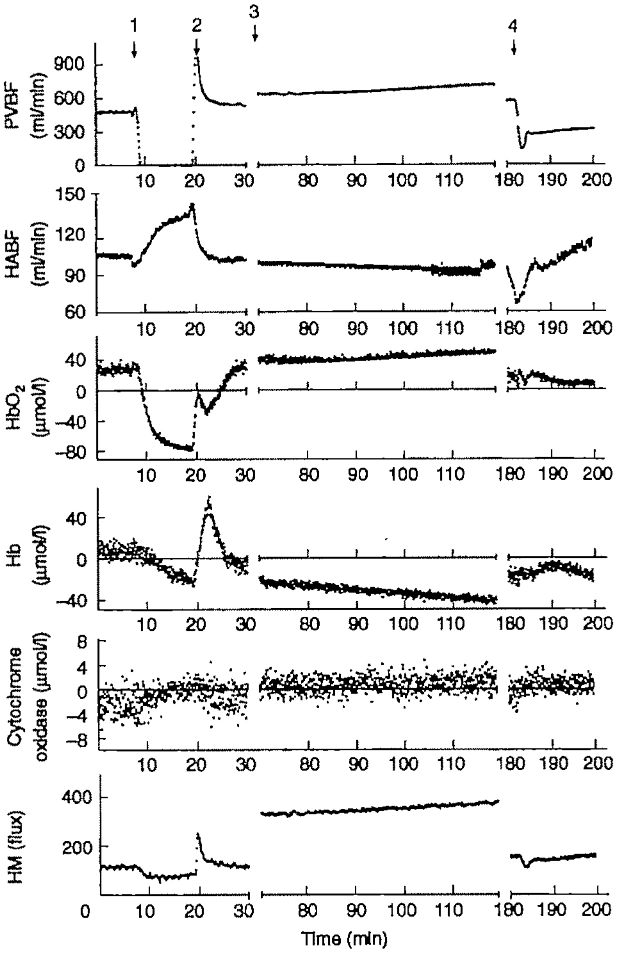

Fig. 2 Typical example of the effect of pump insertion on hepatic haemodynamic data. 1, Portal vein clamping to allow pump insertion; 2, restoration of baseline portal vein flow; 3, pump started; 4, pump stopped. PVBF, portal vein blood flow; HABF, hepatic artery blood flow; HbO_2, oxyhaemoglobin; Hb, deoxyhaemoglobin; HM, flow in the hepatic microcirculation (flux units)

Discussion

This study addressed the technical aspects of surgical insertion of a pump into the portal vein for portal flow augmentation, following the successful development of an impeller pump designed for implantation in humans with cirrhosis[8]. The short-term performance of this pump *in vivo* was assessed, as well as the effect of enhancing portal inflow on flow in the hepatic microcirculation, hepatic tissue oxygenation, and both hepatic and systemic haemodynamics. Operative insertion of the portal pump was achieved successfully with minimal blood loss and no operative morbidity or mortality. The human portal vein is larger than that in the pig, which would facilitate pump insertion. However, pump insertion in a patient with liver disease and portal hypertension is likely to be a considerably greater risk than in a normal healthy pig. The formation of thrombus around the impeller in non-heparinized animals ($n = 3$) suggested the need for anticoagulation in this animal model. In patients with liver cirrhosis the coexistence of coagulopathy may increase the risk of haemorrhage during operation but may prevent the development of thrombus around the pump impeller. Despite the presence of thrombus in some animals the portal inflow was constant throughout the 2 h of augmented portal flow, suggesting that the lumen of the pump remained patent.

There was a strong correlation between the pump speed and flow in the portal vein. When the pump was stopped to simulate an electrical or mechanical failure, there was a drop in portal inflow of 48 per cent, which was associated with a simultaneous reduction in flow in the hepatic microcirculation and in hepatic tissue oxygenation. As a result of the design of the pump, portal venous flow remained at 52 per cent of baseline with flow through the pump even when the motor stopped. This has important clinical implications: should the pump fail *in vivo* the portal blood flow to liver would be reduced but might be sufficient to allow time for correction of the fault.

An increase of portal inflow of about 50 per cent was achieved. Further increase in the pump speed resulted in a sudden drop in portal vein flow associated with a visible collapse of the portal vein on the inflow side of the pump, indicating an insufficient venous reservoir from the mesentery. Blood flow in the portal vein is of low frequency waveform and non-pulsatile. Mechanical pumping of portal venous blood on the other hand produced a pulsatile portal venous flow similar to that of the hepatic artery. This alteration of the normal flow pattern in the portal vein may be a beneficial factor in perfusion of the cirrhotic liver and for the prevention of venous thrombosis[6].

In the hepatic arterial buffer response, a decrease in the portal venous inflow results in an increase in the hepatic arterial flow due to a local effect of adenosine, in order to maintain constant total hepatic tissue oxygenation[16]. Augmenting portal venous flow in this study was associated with a small and non-significant reduction in hepatic arterial blood flow such that the overall effect of pumping was to produce a significant increase in hepatic tissue oxygenation. Flow in the hepatic microcirculation was related directly to blood flow in the portal vein. With increased delivery of blood to the liver parenchyma, the hepatic extracellular tissue oxygenation increased linearly. This is likely to improve the delivery of oxygen and nutrients to the liver and may explain the functional improvement seen in a cirrhotic animal model[6]. In liver cirrhosis there is abnormal hepatic microcirculation and decreased substance diffusion through sinusoids as a result of capillarization[17–19]. With improved hepatic microcirculation and tissue oxygenation, an improvement in liver function might be expected in patients with cirrhosis. This concept has been suggested by *in vivo* data in cirrhotic animal models[5,6]. Portal vein flow augmentation has been shown to reduce portal vein pressure in a perfused cirrhotic animal model[1,4,6], suggesting a possible role in reducing variceal pressure and prevention of haemorrhage. It has also been shown to improve diffusion through the liver sinusoids[2].

During this short period of portal pumping in a normal large animal model, there were no systemic haemodynamic effects. In portal hypertension there are often gross portosystemic collaterals. Bernadich *et al.*[5] demonstrated that augmenting the portal inflow did not increase the risk of shunting or change the systemic haemodynamics, indicating the extra blood flow had derived from the collaterals. Most of the drugs used for treatment of portal hypertension interfere with the systemic circulation leading to a reduction in cardiac output and worsening of renal function[20,21]. If reproducible in humans, the avoidance of systemic upset by portal flow augmentation would have many advantages over drug therapy for portal hypertension.

An implantable portal venous pump could be used clinically as sole therapy or as a bridge to orthotopic liver transplantation. With the current shortage of donor organs the wait for orthotopic liver transplantation is increasing. Further developments for the implantable pump include the use of biopolymers and heparin coating to prevent thromboembolism, and a small rechargeable battery for long-term use. The insertion of the portal pump was achieved in this experiment by laparotomy and a venotomy. In patients with cirrhosis or portal hypertension laparotomy is associated with significant mortality and morbidity, and damage to the portal vein may prohibit liver transplantation. The developers are pursuing the option of percutaneous or transjugular insertion.

In conclusion, this portal pump, which has been developed for human implantation, was inserted successfully into the main trunk of the portal vein in a large animal. Flow in the hepatic microcirculation and tissue oxygenation was related directly to the portal inflow. Long-term assessment of the value of the portal pump in a cirrhotic animal model is required to study the full impact of portal pumping on systemic and hepatic haemodynamics, and its biocompatibility.

Acknowledgements

The authors thank Dr M. Pignatelli at Imperial College for reading the histology slides, Mr D. Moore and staff in the

Comparative Biology Unit at the Royal Free and University College Medical School for providing expertise in animal care and anaesthesia, and Dr R. Morris, Academic Department of Public Health and Primary Care, Royal Free and University College Medical School, for providing statistical advice. They are also grateful to all EEC technical partners for development of the implantable pump, especially Mr O. Marseille and Professor W. Kerkhoffs of the Institute of Helmholtz, University of Technology, Aachen, Germany. This work was supported by an EEC grant (ESPRIT III IMALP project, no. 21245). The Royal Free Hospital Special Trustees purchased the dual Transonic Medical Flowmeter system.

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Original article

Analysis of 153 gunshot wounds of the liver

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Background: Gunshot wounds of the liver may result in substantial morbidity and death, and optimal management of complex injuries is controversial.

Methods: One hundred and fifty-three patients with civilian gunshot liver injuries were treated during the 10-year period 1986–1995. Demographic, clinical and operative data were recorded. Factors influencing postoperative complications and death were analysed.

Results: One hundred and forty-two patients (93 per cent) had single missile injuries and 11 (7 per cent) had shotgun injuries. Three patients were treated non-operatively and 150 patients underwent operation. In 105 patients (70 per cent) the injuries to the liver were minor and required either no treatment (93) or simple suture of bleeding vessels (12). Forty-five patients (30 per cent) had major injuries which were either packed only (26) or required more complex surgical intervention (19). This included resectional debridement (ten), major venous repair (eight) and hepatotomy (one); eight of these patients required packing combined with the procedure. Associated intra-abdominal injuries occurred in 115 patients (77 per cent). The overall mortality rate was 17 per cent (26 patients). Death was directly attributable to the liver injury in 13 patients (8 per cent), 12 of whom died from uncontrolled bleeding. Complications occurred in 63 (51 per cent) of 124 survivors, and correlated with the type and severity of the liver injury and the number of associated injuries.

Conclusion: Most gunshot liver injuries can be managed by simple surgical techniques. In complex injuries control of major haemorrhage is vital and perihepatic packing may be life saving before undertaking definitive repair of the injury under controlled conditions.

Paper accepted 22 February 2000

British Journal of Surgery 2000, 87, 1030–1034

Introduction

The liver is the most commonly injured solid organ in patients with abdominal gunshot wounds[1]. The principal objectives in the treatment of liver trauma are early and effective control of bleeding, with preservation of hepatic function and prevention of septic and ischaemic complications. Most injuries are uncomplicated and can be managed by well established basic surgical techniques, including cautery, temporary packing, suture and vessel ligation[1–6]. However, in patients with complex liver injuries, the operative mortality rate still exceeds 40 per cent even in trauma referral centres[5–9]. The leading cause of death in severe liver injuries is uncontrollable bleeding, while multiple organ failure and residual sepsis are the primary causes of late death and morbidity[3–5,10].

In the past decade there has been substantial change in the management of complex liver injuries. Important refinements have included the re-emergence of temporary liver packing[10], hepatotomy and direct vascular suture[2,5], the use of hepatic inflow control[9,11,12] and total hepatic isolation in major venous injuries[13], and the use of limited debridement rather than major liver resection[14]. Further advances and techniques include selective non-operative management[15], laparoscopic evaluation of the extent of injury[16], a clearer understanding of hepatic segmental and vascular anatomy and hepatic tolerance to normothermic ischaemia[9], improved postoperative intensive care, the utilization of both diagnostic and interventional radiology, and the application of an integrated and multidisciplinary approach to the management of patients with complex injuries[17]. Despite these developments, in the absence of a universally accepted treatment algorithm, there remains a wide diversity in this approach[12–14,18,19]. This report analyses the outcome of gunshot liver injuries treated at a major hepatobiliary trauma centre during a 10-year period with the objective of evaluating the efficacy of current methods of treatment.

Patients and methods

One hundred and fifty-three consecutive civilian patients with gunshot injuries of the liver were treated at Groote Schuur Hospital, one of two major trauma referral centres serving a population of 1·5 million in the greater Cape Town metropolitan area, during the 10-year period 1986–1995. Analysis involved a retrospective review of patient information in the hepatopancreatobiliary and trauma unit liver injury database. One hundred and forty-two patients had low-velocity single missile injuries and 11 had shotgun injuries. There were 141 men and the mean age was 32 (range 14–65) years. The initial evaluation and management of all patients admitted with abdominal trauma was in accordance with American College of Surgeons Advanced Trauma Life Support principles[20]. Liver injuries were graded according to the American Association for the Surgery of Trauma (AAST) Hepatic Injury Scale[21].

Operation

Exploratory laparotomy was performed when peritoneal penetration was suspected. Bleeding from minor or superficial injuries was controlled by simple operative techniques which included temporary compression with packs or diathermy. Mattress sutures or ligation of visible bleeding vessels within the laceration were used if manual compression failed. Profuse bleeding from deep wounds was controlled by occluding vascular inflow in the hepatoduodenal ligament below the porta hepatis with a vascular clamp (Pringle manoeuvre[11]). Deep lacerations were inspected carefully after retraction of the edges to allow individual ligation of the bleeding vessels. If exposure or access was inadequate, the laceration was extended by finger fracture ('hepatotomy') to enable suture ligation of the bleeding point and parenchyma was preserved whenever possible[2]. Only devitalized tissue was removed by non-anatomical resectional debridement using the finger fracture technique along the line of injury.

Packing

For persistent bleeding four to six abdominal packs were placed above and below the liver to staunch blood loss and provide haemostasis by tamponade[10]. Patients were then returned to the operating room after 48 h for removal of the packs and, if necessary, repair of any bleeding vessels[5,10]. If gross bowel contamination or bile leaks were identified during initial surgery and packing was unavoidable, packs were retrieved at relaparotomy within 24 h[10].

Postoperative care

Patients with postoperative pyrexia and suspected intra-abdominal collections underwent ultrasonography or computed tomography with a view to percutaneous aspiration or catheter drainage of intraperitoneal collections. Laparotomy was used where collections were inaccessible to percutaneous drainage. Persistent bile fistulas were investigated by endoscopic retrograde cholangiopancreatography, and sphincterotomy and endoscopic biliary stenting was used when a bile leak was demonstrated.

Results

One hundred and five (70 per cent) of the 150 patients who underwent laparotomy had liver injuries amenable to simple techniques (*Table 1*). Forty-five patients (30 per cent) had complex liver injuries in which the bleeding could not be controlled by temporary packing or simple suture and required more complicated procedures. In 34 patients (23 per cent) therapeutic liver packing was used to control bleeding; 26 patients (17 per cent) had packing alone and eight had a combination of packing and another procedure. At the initial procedure devitalized tissue was debrided in nine (6 per cent) patients and one patient required a formal right hepatic lobectomy after right hepatic artery embolization for persistent haemorrhage.

Eight patients (5 per cent) had major juxtahepatic venous injuries. Primary repair was attempted in seven patients; one patient had initial abdominal packing and returned to the operating theatre 48 h later where hepatotomy was performed, and lacerations to the right and middle hepatic veins were repaired. Control of liver inflow with hepatoduodenal vascular clamping was used in all of these patients, with total hepatic isolation in the last patient.

Associated injuries

Two hundred and thirty-eight associated intra-abdominal injuries occurred in 115 (75 per cent) of the 153 patients. The abdominal organs most commonly injured were stomach in 45 patients (29 per cent), colon in 42 (27 per cent), small bowel in 26 (17 per cent), kidney in 25 (16 per cent), duodenum in 23 (15 per cent) and pancreas in 22 (14 per cent).

Table 1 Operation according to liver injury grade

Liver injury grade	*n*	Operation					
		None	Simple suture	Packing only	Debridement/ resection	Hepatotomy	Venous repair
I	9	9 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
II	17	17 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
III	98	67 (68)	12 (12)	15 (15)	4 (4)	0 (0)	0 (0)
IV	11	0 (0)	0 (0)	7 (64)	4 (36)	0 (0)	0 (0)
V	12	0 (0)	0 (0)	4 (33)	2 (17)	1 (8)	5 (42)
VI	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (100)
Total	150*	93 (62)	12 (8)	26 (17)	10 (7)†	1 (1)	8 (5)

Values in parentheses are percentages. *Three patients treated conservatively are not included. †Nine patients debrided and one formal hepatectomy performed

Complications

Eighty-seven postoperative complications occurred in 63 (50 per cent) of the 127 surviving patients. Fifty-eight (48 per cent) of the 121 survivors with single missile wounds developed complications compared with five of the six survivors with shotgun wounds.

Morbidity directly attributable to the liver injury occurred in 22 patients (17 per cent). Thirteen patients developed a bile leak. Eleven patients had bile leaks from abdominal drains and two patients developed a biliary–pleural fistula through associated diaphragmatic injuries. Five patients developed a bile collection of which four were drained percutaneously and one at laparotomy. Five persistent fistulas were evaluated by endoscopic retrograde cholangiogram (ERC) and an endoscopic sphincterotomy was performed after demonstrating the biliary leak. In two patients a biliary leak persisted, and required a second ERC and insertion of a biliary stent. One patient developed a biliary stricture and required a hepaticojejunostomy after initial suture of a hepatic duct injury. Three patients, who had been packed initially, required reoperation for bleeding; two patients were successfully repacked and one required repair of a major venous injury.

Seventeen patients had septic complications and 11 developed pancreatic (five), enteric (five) or duodenal (one) fistulas. The mean hospital stay in the 23 patients who developed liver-related complications was 22 (range 8–49) days compared with 8 (3–22) days in patients who had no postoperative morbidity.

Deaths

Twenty-six patients (17 per cent) died. Twenty-one (15 per cent) of 142 patients with single missile injuries died compared with five of 11 with shotgun injuries. Fourteen deaths (9 per cent) were directly attributable to the liver injury. Twelve deaths (8 per cent) were due to exsanguinating bleeding from the liver (six) or juxtahepatic major venous injuries (six). One patient died from haemorrhage from both liver and vena caval wounds, and one patient died from hepatic failure after a massive shotgun injury. Of the 13 patients who died from exsanguinating haemorrhage, 11 died in the operating room during the initial operation. Twelve deaths were due to associated lethal injuries, involving heart, brain, lung or aorta. One patient died from a pulmonary embolus. The liver injury-related mortality rate was directly proportional to the severity and grade of the injury (*Table 2*). The total liver-related mortality rate for minor injuries (grades I–III) was 1 per cent (one of 124 patients) compared with 50 per cent (13 of 26 patients) with major injuries (grades IV–VI).

Juxtahepatic major venous injuries

Eight patients (5 per cent) had major juxtahepatic venous injuries of whom six died. Two of three patients with injuries involving both the retrohepatic inferior vena cava (IVC) and hepatic veins died. Three patients had complete disruption of the porta hepatis; one patient also had injury to the IVC. All three patients died, either on the operating table (two) or within 24 h (one).

Discussion

The overall mortality rate in 153 consecutive adult civilian liver gunshot injuries in this study was 17 per cent. The number and severity of associated injuries[1,4] as well as liver and juxtahepatic venous bleeding were the major factors determining outcome, and contributed to the higher mortality rate in higher AAST grades in this and other series[22,23]. Half of the deaths were directly attributable to

Table 2 Mortality and morbidity rates according to liver injury grade

Liver injury grade	*n*	Overall deaths	Liver-related deaths	Survivors	Survivors with complications	Liver-related complications
I	9	0 (0)	0 (0)	9 (100)	3 (33)	1 (11)
II	17	2 (12)	0 (0)	15 (88)	8 (53)	0 (0)
III	98	10 (10)	1 (1)	88 (90)	44 (50)	16 (18)
IV	11	2 (18)	2 (18)	9 (82)	5 (56)	3 (33)
V	12	9 (75)	8 (67)	3 (25)	3 (100)	3 (100)
VI	3	3 (100)	3 (100)	0 (0)	—	—
Unknown*	3	0 (0)	0 (0)	3 (100)	1 (33)	1 (33)
Total	153	26 (17)	14 (9)	127 (83)	64 (50)	24 (19)

Values in parentheses are percentages. *Treated non-operatively

the liver injury, and the remainder were due to associated injuries; mortality rates were similar to those of liver gunshot injuries from other centres[4]. Close-range shotgun injuries were associated with a 36 per cent mortality rate and 71 per cent morbidity rate compared with 15 and 48 per cent respectively following single-missile gunshot wounds.

Rapid control of liver bleeding is critical and temporary liver packing with manual compression in this situation is now an established life-saving manoeuvre while resuscitation is continued[3,10,24]. When conventional haemostatic procedures fail to control bleeding in a patient with recalcitrant coagulopathy, hypothermia and acidosis, perihepatic packing has an important role as a definitive procedure[10,12,24]. Intra-abdominal packing of major liver injuries also facilitates transfer from a peripheral hospital to a tertiary centre for definitive management[24]. Twenty-six patients in this study required therapeutic packing for persistent bleeding from major injuries, with effective control of bleeding in all but three.

The most devastating gunshot wounds of the liver involve the retrohepatic IVC, portal and hepatic veins, and patients present with profound hypovolaemic shock and a tense haemoperitoneum[1,4,5]. The high mortality rate in this (six of eight patients) and other[4,5,25] series, despite left thoracotomy and cross-clamping of the aorta before laparotomy, has led to a revised surgical strategy in major juxtahepatic venous gunshot injuries. The current protocol in this unit is to perform an urgent resuscitative laparotomy, pack the liver and continue intraoperative resuscitation while an experienced hepatobiliary surgeon is summoned. Bleeding despite control of the hepatic inflow suggests a major hepatic vein or juxtahepatic vena caval injury. This can often be controlled by perihepatic packing with no further bleeding after subsequent delayed pack removal[10].

The role of hepatic resection for complex liver injuries is controversial. Of the ten patients in this study who required resection, nine had resectional debridement of non-viable liver adjacent to the injured site and one required a major anatomical resection. Some authors remain enthusiastic about major hepatic resection in complex liver injuries[17,26,27] despite a reported mortality rate ranging from 40 to 60 per cent[7,14,26]. The present authors believe that a more conservative approach is more than justified. Liver parenchyma that is clearly devitalized needs debridement. However, formal hepatic lobectomy should be reserved for the few selected patients with major burst injuries and associated extensive lobar devitalization seen more commonly with high-impact blunt trauma[25] and in close-range shotgun injuries. Many authors now adopt a more conservative approach to anatomical hepatic resection in major liver trauma[3,14].

Multidisciplinary management of the late complications of gunshot liver injuries has become an integral component of the complete management of liver trauma. Ultrasonography, percutaneous aspiration or catheter drainage, angiographic embolization and interventional endoscopy to identify and manage septic, arterial or biliary complications of liver injuries are essential elements in the management of these injuries in the modern era[4,12,27]. In this study four patients had bile collections drained percutaneously under ultrasonographic guidance. Endoscopic sphincterotomy was reserved for patients with a significant bile leak that persisted longer than 14 days.

Most gunshot injuries of the liver required no treatment at laparotomy or could be managed successfully with minimal surgical intervention. In major liver gunshot injuries, however, the greatest immediate threat to life is exsanguinating haemorrhage. Rapid control of bleeding is the priority. Haemostasis is best achieved with optimal exposure and a well organized plan of management. Major liver injuries are packed using abdominal swabs and bleeding staunched by manual compression to allow effective resuscitation while awaiting the arrival of skilled surgical and anaesthetic assistance. Packing is also used as a definitive measure in peripheral hospitals with limited resources to allow transfer to a major centre, in selected patients with retrohepatic venous injuries or at the earliest sign of coagulopathy. When lacerations bleed profusely, the key to management is initial temporary portal triad control. The authors recommend hepatotomy with finger fracture extension of the liver injury to expose inaccessible bleeding vessels within deep parenchymal lacerations, and control of bleeding by suture ligation or vascular repair under direct vision as the definitive method of choice. Failure of inflow control suggests major retrohepatic venous injury. In this situation liver bleeding is directly approached using total hepatic isolation which is reserved for control and repair of major hepatic vein or caval injuries. Sternotomy, thoracotomy and atriocaval shunting techniques are now seldom used. Early recognition of the magnitude of complex injuries and access to a tertiary facility with a dedicated hepatobiliary surgical team experienced in liver trauma are now regarded as essential requirements in the management of major injuries.

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Original article

Expression and processing of gastrin in pancreatic adenocarcinoma

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Background: Gastrin is a trophic hormone and promotes growth of gastrointestinal and non-gastrointestinal cancers. Studies both *in vitro* and *in vivo* have suggested that pancreatic cancer cells not only have the ability to respond to circulating forms of gastrin but also to respond to the autocrine production of gastrin and its precursors. The aim of this study was to identify the expression of CCK-B/gastrin receptor, progastrin, glycine-extended gastrin and amidated gastrin in both normal pancreas and pancreatic adenocarcinoma.

Methods: Tissue sections from patients with normal pancreas ($n = 10$) and pancreatic cancer ($n = 22$) were assessed using immunohistochemical methods for CCK-B/gastrin receptor, progastrin, glycine-extended gastrin and amidated gastrin expression.

Results: Normal pancreas showed no expression of receptor or gastrin isoforms except for occasional cells in the islets. Definite expression of CCK-B/gastrin receptor, progastrin, glycine-extended gastrin and amidated gastrin was observed in 95, 91, 55 and 23 per cent of sections from patients with pancreatic cancer respectively.

Conclusion: Pancreatic cancer cells express CCK-B/gastrin receptor and gastrin precursor forms in most patients. Expression of the gastrin precursor forms is probably related to autocrine production. New therapeutic strategies need to be developed for the management of pancreatic cancer. Targeting gastrin and its receptor may provide a novel treatment option.

Paper accepted 22 February 2000

British Journal of Surgery 2000, **87**, 1035–1040

Introduction

Gastrin is a trophic hormone in the gastrointestinal tract. It has been shown to promote the growth of both normal gastrointestinal mucosa[1] as well as gastrointestinal cancers including colon cancer[2] and stomach cancer[3]. Gastrin also has been shown to promote the growth of pancreatic carcinoma[4], hepatocellular carcinoma[5], renal cell carcinoma[6] and small cell carcinoma of the lung[7].

Cell culture studies and animal models suggest that, as for gastrointestinal and hepatocellular cancers, pancreatic adenocarcinoma cells not only have the ability to respond to circulating forms of gastrin but also respond to the autocrine production of gastrin and its precursors[8]. The ability to synthesize forms of gastrin is dependent on the cellular machinery for post-translational processing of precursor gastrin. In basic terms, this is predominantly an enzymatic process resulting in the cleavage of preprogastrin by endopeptidase to progastrin, which is further processed to glycine-extended gastrin 34. The glycine-extended gastrin 34 can be amidated by peptidylglycine α-amidating mono-oxygenase to form amidated gastrin 34, or cleaved at dibasic residues resulting in the formation of amidated gastrin 17 and glycine-extended gastrin 17[9]. Cells are able to respond to the mature amidated forms of gastrin and also to the precursor forms, especially glycine-extended gastrin[10]. The relative importance of the circulating isoforms of gastrin and the forms produced by cells in an autocrine fashion has still to be established.

The editors have satisfied themselves that all authors have contributed significantly to this publication.

Table 1 Expression of CCK-B/gastrin receptor, progastrin, glycine-extended gastrin and amidated gastrin in normal pancreas ($n = 10$)

Antibody	Intensity of staining in normal pancreas
CCK-B/gastrin receptor	Occasional cells in islets/no staining of acinar cells
Progastrin	Occasional cells in islets/no staining of acinar cells
Glycine-extended gastrin	Occasional cells in islets/no staining of acinar cells
Amidated gastrin	Occasional cells in islets/no staining of acinar cells

The aim of this study was to identify the expression of CCK-B/gastrin receptor, progastrin, glycine-extended gastrin and amidated gastrin in both normal pancreas and pancreatic adenocarcinoma.

Patients and methods

Pancreatic tissue sections

Paraffin sections 5 μm thick from consecutive unselected patients at the Royal Free Hospital with pancreatic carcinoma ($n = 22$) and normal pancreatic biopsies ($n = 10$) were assessed.

Immunohistochemistry

Tissue sections were dewaxed in xylene (Chemicon, Harrow, UK) for 10 min, dehydrated in 100 per cent alcohol and rinsed in double-distilled water for 5 min. For detection of gastrin receptor and amidated gastrin, slides were microwaved in citric acid buffer 0·01 mol/l for 5 min. No pretreatment was used for progastrin or glycine-extended gastrin detection. All sections were incubated in 15 per cent acetic acid for 20 min to inhibit endogenous alkaline phosphatase activity. Non-specific binding was blocked by incubating the sections in 10 per cent normal goat serum (DAKO, High Wycombe, UK) in tris-buffered saline (TBS; Sigma, Poole, UK) for 15 min. Optimally diluted antibody (see below) was added to each section for 1 h. Control studies were performed without primary antibody and by preabsorbance of antibody with epitope. Binding was detected using alkaline phosphatase-conjugated goat antirabbit antibody (Sigma) at a dilution of 1 : 50 in TBS for 1 h at room temperature. Sections were washed in TBS for 5 min then visualized using fast red (Sigma) as chromogen, incubating at room temperature for 10–20 min. Sections were counterstained in Carrazi's haematoxylin, air dried and mounted in Loctite UV adhesive (Loctite, Welwyn Garden City, UK).

Antibodies

CCK-B gastrin receptor antibody (dilution 1 : 100) is a rabbit polyclonal antibody raised against the amino-terminal sequence of the human CCK-B/gastrin receptor[11].

Progastrin antibody (dilution 1 : 300) is a rabbit polyclonal antibody raised against human preprogastrin; it reacts with carboxy-terminal progastrin fragments longer than hexapeptide[12].

Glycine-extended gastrin antibody (dilution 1 : 200) is a rabbit polyclonal antibody raised against human carboxy-terminal glycine-extended gastrin; it reacts equally with glycine-extended gastrin 17 and glycine-extended gastrin 34[12].

Gastrin antibody (dilution 1 : 200) is a rabbit polyclonal antibody raised against human carboxy-terminal amidated gastrin 17; it reacts with carboxy-terminal amidated gastrin 34 (DAKO).

Immunohistochemical scoring

All sections were scored independently by two experienced histopathologists. The interobserver and intraobserver variation was below 10 per cent. Where there was variation in score the section was jointly reviewed and a score agreed. Immunostaining was scored as strong, moderate, weak or no staining.

Results

Normal pancreas showed no expression of CCK-B/gastrin receptor, progastrin, glycine-extended gastrin or amidated gastrin except for occasional cells in the islets (*Table 1*, *Fig. 1*). Pancreatic cancer cells showed definite expression (moderate or intense) of the CCK-B/gastrin receptor in 95 per cent, progastrin in 91 per cent, glycine-extended gastrin in 55 per cent and amidated gastrin in 23 per cent of cancer sections (*Table 2*, *Fig. 2*). Pancreatic cancer was often seen in the region of nerve fibres (*Fig. 3*).

Discussion

This study has demonstrated that pancreatic adenocarcinoma expresses the CCK-B/gastrin receptor as well as precursor forms of gastrin, especially the progastrin and glycine-extended forms. This is similar to findings for other cancers including gastric[13], colonic[14] and hepatocellular[15] carcinomas.

Gastrin is known to be transiently expressed in foetal pancreas; it is associated with pancreatic growth and

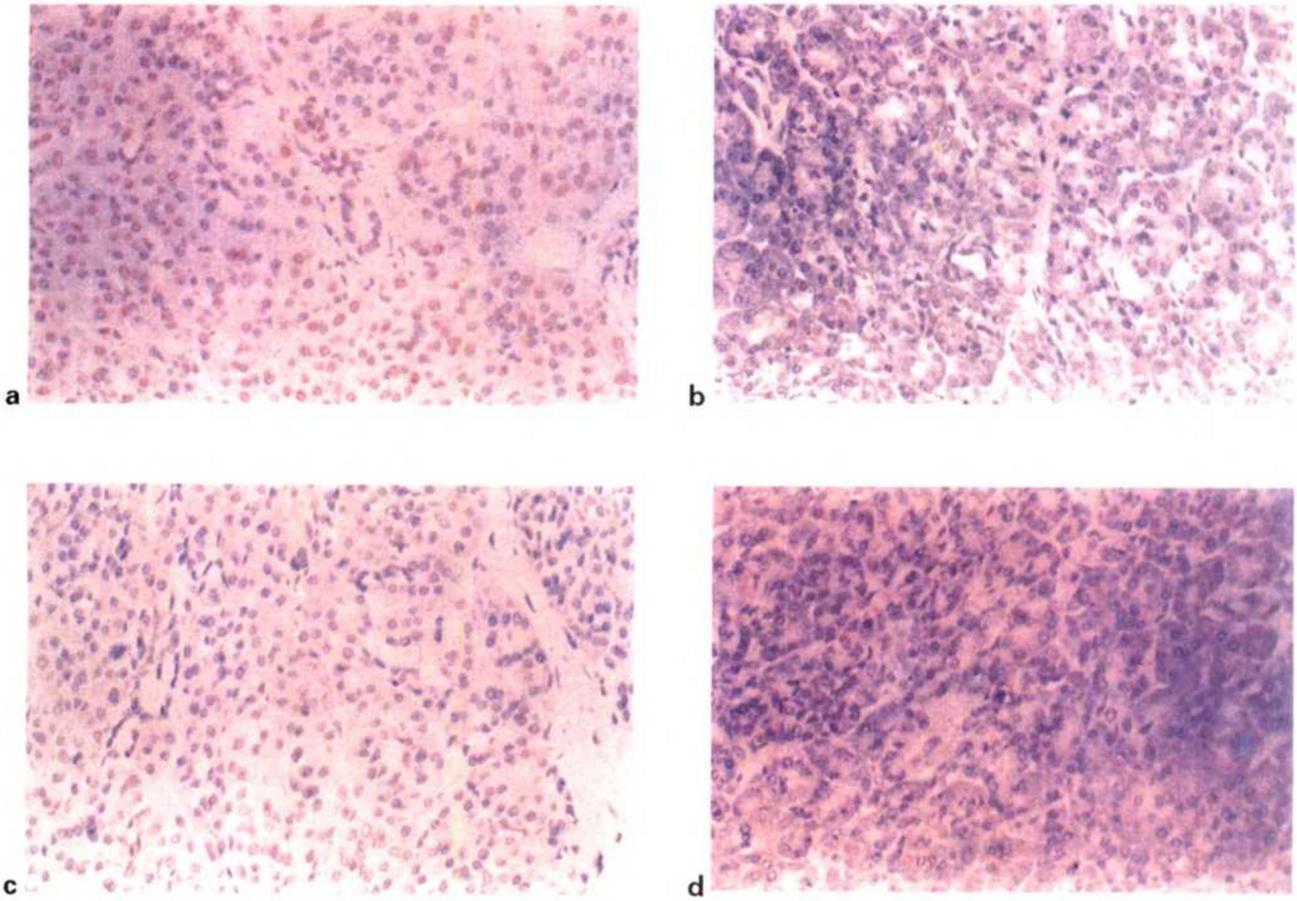

Fig. 1 Alkaline phosphatase red immunohistochemistry of normal pancreas demonstrating no expression of **a** CCK-B/gastrin receptor, **b** progastrin, **c** glycine-extended gastrin and **d** amidated gastrin. (Original magnification × 200)

Table 2 Expression of CCK-B/gastrin receptor, progastrin, glycine-extended gastrin and amidated gastrin in pancreatic cancer ($n = 22$)

	Intensity of tumour staining			
Antibody	None	Weak	Moderate	Strong
CCK-B/gastrin receptor	0	1	18	3
Progastrin	1	1	14	6
Glycine-extended gastrin	4	6	12	0
Amidated gastrin	15	2	5	0

differentiation but does not appear to be expressed in the normal adult pancreas[16,17]. Many tumours have an oncofoetal expression of peptides and this may apply in relation to gastrin and the pancreas.

Gastrin has been shown to promote the growth of pancreatic adenocarcinoma cell lines *in vitro*[18], and also *in vivo* in the rat using azaserine induction of pancreatic adenocarcinoma[19] as well as in mouse xenograft models[20]. Antigastrin agents including CCK-B/gastrin receptor antagonists have been shown to inhibit tumour proliferation in both *in vitro* and *in vivo* models[20,21].

There is some controversy in the literature about whether the CCK-B/gastrin receptor is expressed in normal human pancreatic tissue and pancreatic adenocarcinoma[22,23]. In the present study only a minority of islet cells in the normal pancreas and no acinar cells expressed the CCK-B/gastrin receptor and gastrin forms. This suggests that in neoplastic pancreatic tissue gastrin gene expression is switched on, which would fit with the hypothesis of oncofoetal expression of gastrin.

It has been established previously that gastrin stimulates the growth of pancreatic cancer by an autocrine mechanism[7,21]. There is constitutive release of amidated gastrin and its precursor forms, which feed back not only to their own cell but also to neighbouring cells thus having a paracrine effect. Amidated gastrin binds to the CCK-B/gastrin

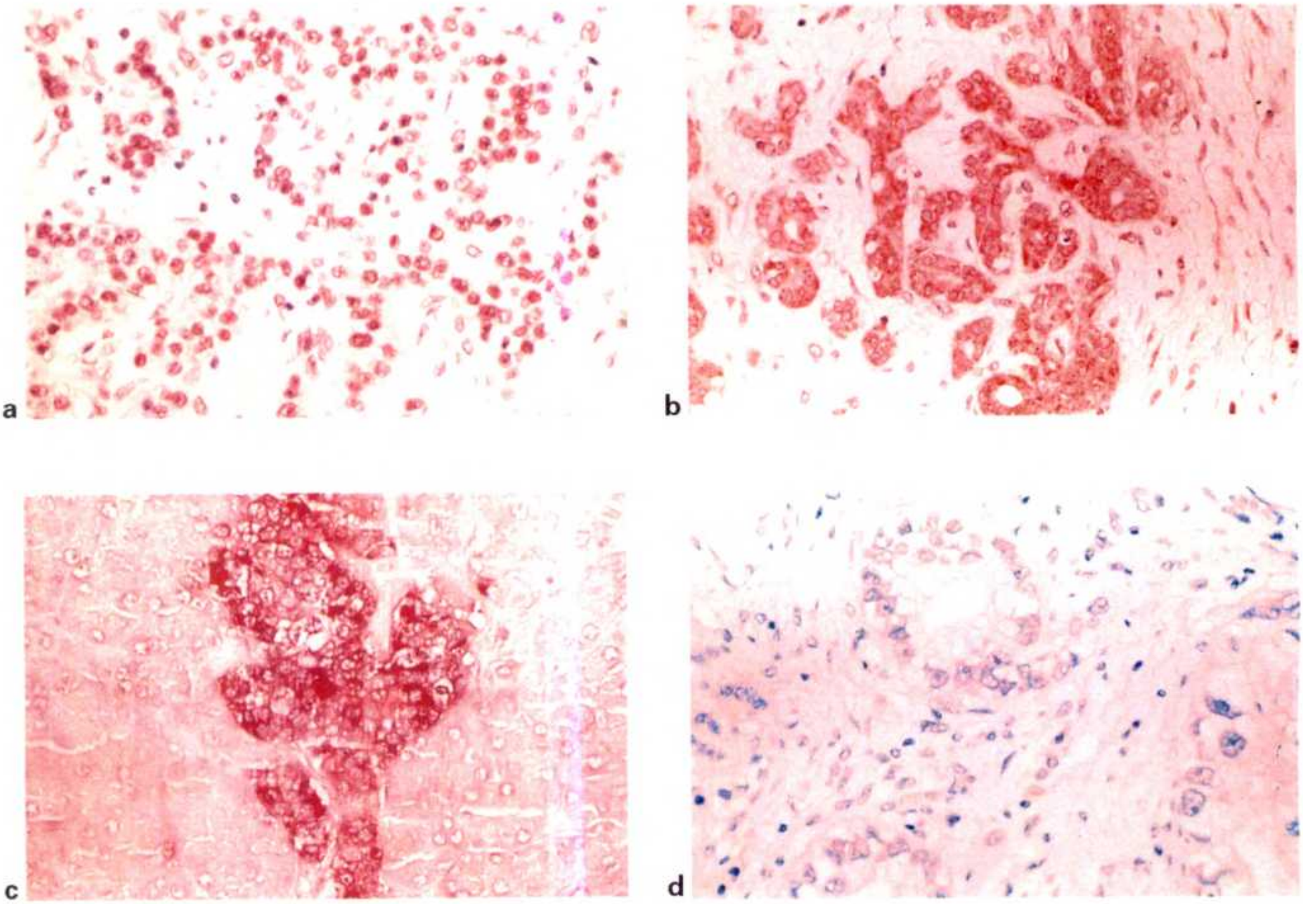

Fig. 2 Alkaline phosphatase red immunohistochemistry of pancreatic cancer demonstrating expression of **a** CCK-B/gastrin receptor, **b** progastrin and **c** glycine-extended gastrin but no expression of amidated gastrin (**d**). (Original magnification × 200)

receptor but the precursor forms bind to an as yet uncharacterized 'CCK-C' receptor. These precursor forms of gastrin have also been shown to be trophic in their own right and may be even more potent than amidated gastrin[24].

Studies using CCK-B/gastrin receptor antagonists have demonstrated inhibition of pancreatic cancer cell proliferation both *in vivo* and *in vitro*. There are currently no 'CCK-C' receptor antagonists, but antigastrin antibodies which bind both amidated and glycine-extended forms of gastrin inhibit the proliferative effect of glycine-extended gastrin in pancreatic cancer[7,21].

Transgenic mouse models provide supporting evidence for the trophic effects of gastrin at the gene level. These involve fusion of a simian virus 40 large tumour antigen (SV40 Tag) gene to a 1·5-kilobase 5′ flanking region of the gastrin gene or the SV40 Tag gene fused to a 10·5-kilobase mid-region of the gastrin gene; both result in the mice developing pancreatic tumours[25].

In this study most pancreatic cancer specimens expressed progastrin, but only 55 per cent definitely expressed glycine-extended gastrin and 23 per cent amidated gastrin. This is almost certainly a conservative estimate owing to the limited sensitivity of immunohistochemistry. However, the relative lack of mature amidated gastrin is probably a reflection of the cellular machinery within tumours; the cancer cell often does not have the capability, associated with the enzymatic pathway, for fully processing the precursor forms of gastrin. Recently Hollande *et al.*[26] suggested that, in addition to the 'classical' extracellular autocrine loop, there is an intracellular, intracrine loop where progastrin within the cell binds to intracellular receptors to stimulate cell proliferation.

Smith *et al.*[27] reported a twofold increase in fasting serum gastrin and tenfold greater receptor binding capacity in patients with pancreatic cancer compared with normal subjects. They postulated that the aggressive behaviour of

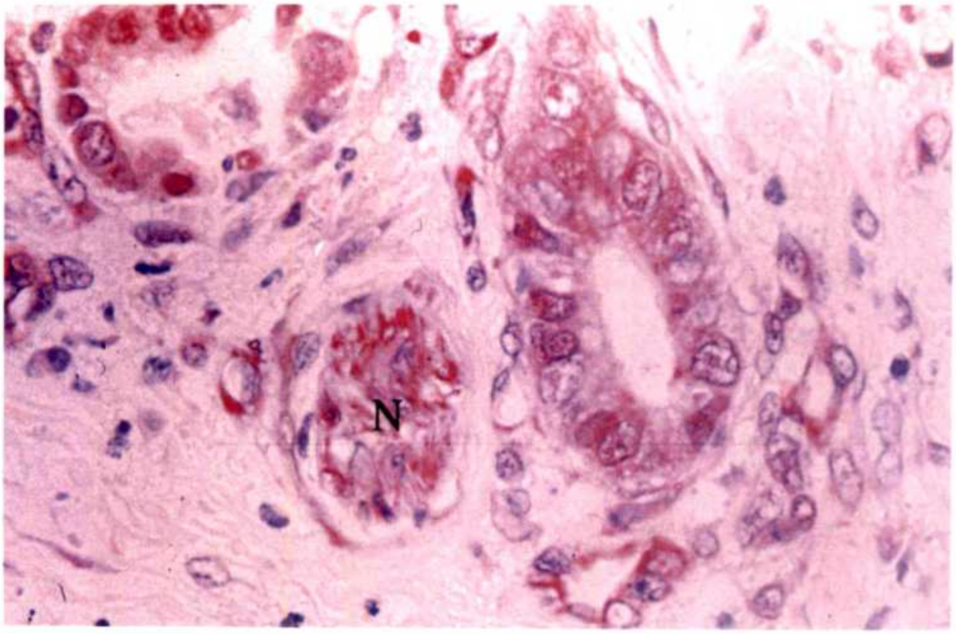

Fig. 3 Alkaline phosphatase red immunohistochemistry of pancreatic cancer stained for progastrin shown in close proximity to a nerve (N). The nerve fibres themselves show some expression of the peptide. (Original magnification × 300)

pancreatic adenocarcinoma may be attributable to the autocrine production of gastrin and to the presence of its growth-related receptor.

It is recognized that pancreatic cancer cells are often found in the proximity of nerves. A number of studies have shown that pancreatic cancer infiltrates local nerves[28]. Dang *et al.*[29] found that pancreatic cancer invaded 73 per cent of pancreatic nerve fibres and also metastasized along nerve fibres in 60 per cent of cases. The proposed explanations for this include mechanical extension along planes of least resistance such as the perineural space[30] and, more recently, that specific factors including peptides enhance the intimate relationship of cancer cells and nerves[31]. The latter explanation has been proposed in relation to transforming growth factor and epidermal growth factor as well as to their receptors. It is conceivable that this hypothesis could also apply to gastrin as it also is a neuropeptide.

Pancreatic cancer has a poor prognosis and none of the currently available therapies offers a significant survival advantage. New therapeutic strategies need to be developed. This study supports the concept that targeting gastrin and its receptor may provide a novel treatment option.

Acknowledgements

The authors thank Dr S. Grimes and Dr D. Michaeli for development and purification of the CCK-B/gastrin receptor antibody, and Professor R. Pounder for contributing to design and the editing of the paper. This study was funded by a research grant from Aphton Corporation, Woodland, California, USA

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Original article

Diagnosis and management of cystic pancreatic tumours with mucin production

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Background: To aid selection of the most appropriate treatment for intraductal tumours (IDTs) and mucinous cystic tumours (MCTs) of the pancreas, this study describes the clinical and diagnostic features of these tumours and compares the clinicodiagnostic features of malignant and benign tumours and hyperplasia.

Methods: The clinical features of 28 IDTs (four cases of hyperplasia, six adenomas and 18 adenocarcinomas) and six MCTs (four adenomas and two adenocarcinomas) were studied.

Results: An IDT was found in 24 men and four women with a mean age of 64·5 years, whereas all patients with an MCT were women, with a mean age of 50·8 years. Twenty IDTs were located in the pancreatic head, whereas all MCTs were in the pancreatic body–tail. The mean size of IDTs was smaller than that of MCTs (4·4 *versus* 7·7 cm). The mean size of hyperplastic lesions, adenomas and adenocarcinomas in IDTs were 1·7, 2·9 and 5·4 cm respectively. Hyperplastic IDT lesions were smaller than 2 cm without either mural nodules or dilatation of the main pancreatic duct. IDTs larger than 3 cm with mural nodules and mucin secretion from an enlarged papilla orifice and dilatation of the main pancreatic duct were often adenocarcinomas.

Conclusion: Although follow-up of intraductal hyperplasia is a reasonable approach, other types of IDT and MCT require surgical treatment.

Paper accepted 28 February 2000

British Journal of Surgery 2000, 87, 1041–1047

Introduction

According to the classification of pancreatic carcinoma of the Japanese Pancreatic Society, intraductal tumours (IDTs) and mucinous cystic tumours (MCTs) of the pancreas belong to two different categories of pancreatic exocrine tumour[1]. IDTs are characterized by dilatation of the main or branch of the pancreatic ducts with abundant mucous secretion, whereas MCTs show the formation of large multilocular or unilocular cysts with a thick fibrous capsule[2–5]. Recent advances in imaging diagnostic techniques such as ultrasonography and computed tomography (CT) have helped to identify asymptomatic pancreatic cystic lesions. It is known that these tumours are potentially malignant but also that they have a good prognosis[3–5]. However, there are major problems in the individual management of these cases as the most appropriate treatment has not yet been established owing to difficulty in differentiating between IDTs and MCTs. Furthermore, preoperative determination of the benign or malignant nature of such tumours is often difficult.

In this study, the clinical differences between IDTs and MCTs are described, as well as various features that may differentiate between benign and malignant tumours, in order to facilitate the selection of appropriate treatment.

Patients and methods

Between November 1984 and January 1998, 34 patients with cystic pancreatic tumours with mucin production were treated at the First Department of Surgery, Okayama Medical University. These tumours were classified into IDTs and MCTs, based on the classification of pancreatic carcinoma by the Japanese Pancreatic Society[1].

IDTs consist of papillary structures lined by tall columnar epithelial cells in the pancreatic duct that show various degrees of cystic dilatation with abundant mucin (*Fig. 1*). In contrast, MCTs contain a large cavity filled with mucous fluid and have a thick fibrous capsule (*Fig. 2*). According to the histological grades of atypia, IDTs were divided into three groups: hyperplasia, adenoma and adenocarcinoma. On the other hand, MCTs consisted of

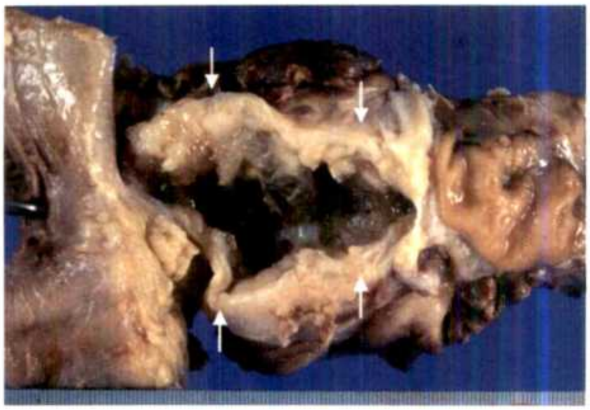

Fig. 1 Gross features of an intraductal tumour. The main pancreatic duct (arrows) is markedly dilated, and is opened longitudinally. Part of the mucosal surface of the main pancreatic duct is granular

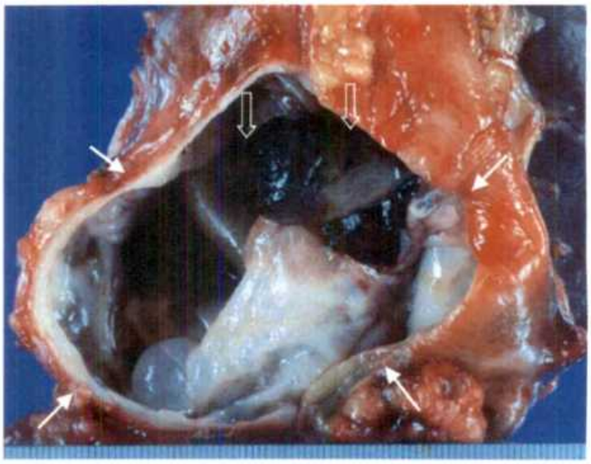

Fig. 2 Gross features of a mucinous cystic tumour. A mural nodule (open arrows) is seen in the cystic cavity (closed arrows) within a thick fibrous capsule

adenomas and adenocarcinomas. Hyperplasia represented lesions with tall columnar epithelial cells in which small and equally sized nuclei were present along the basement membrane but nuclear atypia was absent. Adenomas showed histological features intermediate between hyperplasia and adenocarcinoma; nuclear polarity was still present but a variable degree of nuclear atypia was present. Malignant cells showed loss of nuclear polarity and nuclei of various sizes. IDTs were classified into three subtypes based on their principal location: main pancreatic duct type, branch duct type and mixed type[1] (*Fig. 3*).

The medical records were reviewed to determine the age, sex, symptoms, and serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9. Preoperative imaging included ultrasonography, CT, magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography. CT and ultrasonography were performed in all cases. MRI was used to distinguish the nature of fluid within cystic tumours (i.e. serous or mucinous)[6]. Duodenoscopy and ERCP served to determine the gross appearance of the ampulla of Vater, the largest diameter of the main pancreatic duct, communication with cystic elements, and filling defects (mural nodule and mucin) in the dilated pancreatic duct or cystic lesion. In IDTs, pancreatoscopy during ERCP was performed to examine the main pancreatic duct. Cytological examination of the pancreatic juice and histopathological examination of biopsy material obtained from the mural nodule during ERCP, as well as cytology of cyst fluid obtained by percutaneous aspiration, were also performed. During the later part of the study, the latter procedure was not performed because of concern regarding potential seeding of malignant cells[2]. Tumour size was determined during operation or by measuring the resected specimen.

The χ^2 test with Yates' correction for continuity and the unpaired t test were used to determine statistical differences between groups. $P < 0{\cdot}05$ was considered statistically significant.

Results

There were 28 patients with an IDT and six with a MCT. IDTs included four cases of hyperplasia, six adenomas and 18 adenocarcinomas. MCT comprised four adenomas and two adenocarcinomas.

Clinical features

Patients with IDT included 24 men and four women with a mean age of 64·5 (range 44–78) years (*Table 1*). All patients with a MCT were women, with a mean age of 50·8 (range 37–74) years. Of the 28 patients with an IDT, 18 presented with various clinical symptoms, including abdominal and back pain (15 patients), abdominal mass (one), jaundice (two) and weight loss (one). Of the six patients with a MCT, four had clinical symptoms, including abdominal pain (three) and abdominal mass (two). Ten of 28 patients with an IDT and two of six with a MCT were asymptomatic. In most asymptomatic patients the tumour was detected incidentally by ultrasonography or CT during mass screening or follow-up for other diseases, such as diabetes mellitus. IDTs were commonly located in the head of the pancreas, whereas all six MCTs were located in the body–tail region of the pancreas. The size of IDTs, reflecting the size of the involved dilated pancreatic duct, ranged from 1·4

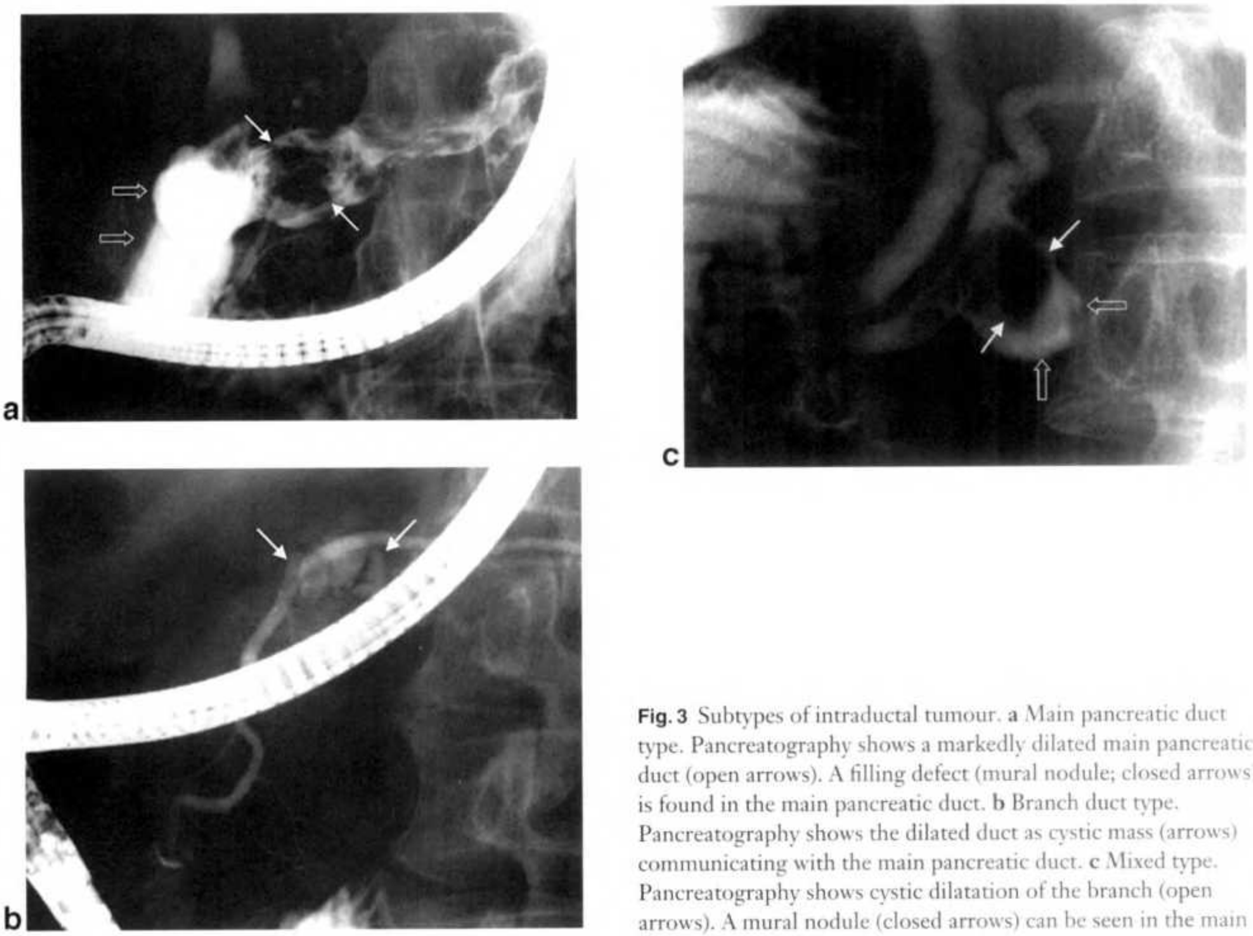

Fig. 3 Subtypes of intraductal tumour. **a** Main pancreatic duct type. Pancreatography shows a markedly dilated main pancreatic duct (open arrows). A filling defect (mural nodule; closed arrows) is found in the main pancreatic duct. **b** Branch duct type. Pancreatography shows the dilated duct as cystic mass (arrows) communicating with the main pancreatic duct. **c** Mixed type. Pancreatography shows cystic dilatation of the branch (open arrows). A mural nodule (closed arrows) can be seen in the main pancreatic duct and its branch

Table 1 Clinical features of patients with cystic pancreatic tumour with mucin production

	IDT ($n=28$)	MCT ($n=6$)	P^*
Mean age (years)	64·5	50·8	< 0·01*
Sex ratio (M : F)	24 : 4	0 : 6	< 0·001†
Symptomatic	18	4	n.s.
Size of tumour (cm)	4·4	7·7	< 0·01*
Location			
Head	20	0	< 0·05†
Body–tail	14	6	
MPD ≥ 5 mm	20	0	< 0·01†

IDT, intraductal tumour; MCT, mucinous cystic tumour; MPD, main pancreatic duct; n.s., not significant. *t test; †χ^2 test

to 9 (mean 4·4) cm, which was smaller than the size of MCTs (range 4–13 (mean 7·7) cm). Thus, compared with IDTs, MCTs tended to be larger, arising from the pancreatic body–tail region in younger women.

ERCP in patients with an IDT showed involvement of dilated pancreatic ducts, in which mural nodules could be seen. Three of five patients with MCT who underwent ERCP showed communication between the cyst and pancreatic duct (*Fig. 4*). ERCP failed to identify mural nodules of MCT because of abundant intracystic mucin. Twenty patients with IDT were found to have dilatation of the main pancreatic duct in excess of 5 mm. Dilatation of the main pancreatic duct was not seen in any patient with MCT.

Malignant signs of intraductal tumours

The mean age of patients with IDT according to histological type (hyperplasia, adenoma and adenocarcinoma) was similar (*Table 2*). Clinical symptoms were present in 16 of 18 patients with adenocarcinoma and in two of ten with benign tumours (hyperplasia and adenoma) ($P < 0{\cdot}01$, χ^2 test). Serum CEA and CA19-9 levels were measured in 26 patients with IDT. As a test for differentiating between malignant and benign tumours, the sensitivity and specificity of serum CEA concentration were 41 and 89 per cent respectively, while serum CA19-9 level had a sensitivity of 41 per cent and a specificity of 100 per cent. With regard to serum levels of tumour markers, CA19-9 concentration tended to be raised in patients with a malignant tumour.

The mean sizes of hyperplasia, adenoma and adenocarcinoma were 1·7, 2·9 and 5·4 cm respectively. In comparing the histological type and the size of tumour, malignancy was found more commonly in tumours greater than 3 cm in diameter than in smaller tumours ($P < 0{\cdot}05$). According to the Japanese classification, IDTs were classified into three subtypes based on the principal location: 12 were in the main pancreatic duct, nine in branch ducts and seven were of mixed type. All IDTs of the main pancreatic duct type were adenocarcinomas. None of four patients with hyperplasia, one of six with adenoma and 15 of 18 with adenocarcinoma showed mucin secretion from an enlarged orifice of the ampulla of Vater ($P < 0{\cdot}001$). Sixteen patients in whom this was found included all 12 patients with tumour in the main pancreatic duct, three of seven with a mixed type of tumour, and one of nine with a branch duct-type tumour. The mean largest diameter of main pancreatic duct was 3 mm in patients with hyperplasia, 4 mm in those with adenoma and 11 mm in patients with adenocarcinoma. No patient with hyperplasia, two with adenoma, and all patients with intraductal adenocarcinoma had dilatation of the main pancreatic duct which exceeded 5 mm ($P < 0{\cdot}001$).

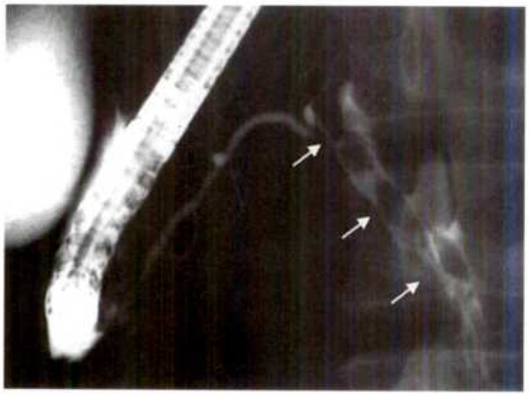

Fig. 4 Pancreatogram of a mucinous cystic tumour (arrows), showing a communication with the main pancreatic duct

Cytological examination of the pancreatic juice and biopsy of a mural nodule during ERCP, or cytology of cystic fluid by percutaneous aspiration, were performed in three patients with hyperplasia, four patients with adenoma and 14 with adenocarcinoma. None of the seven patients with benign lesions had cytological abnormalities characteristic of malignancy, whereas 12 of 14 patients with adenocarcinoma were confirmed to have cytological or histological abnormalities. Preoperative imaging demonstrated mural nodules in cases of intraductal adenocarcinoma, and endoscopic ultrasonography showed mural nodules that could not be detected by other imaging methods. Four of six adenomas in resected specimens consisted macroscopically of a mural nodule, which had not been detected by preoperative imaging. None of the hyperplastic lesions appeared macroscopically as a mural nodule.

Treatment

Tumours were surgically resected by distal pancreatectomy in 14 patients, by pancreatoduodenectomy in eight, by pylorus-preserving pancreatoduodenectomy in four, by duodenum-preserving pancreas head resection in two and by total pancreatectomy in five (*Table 3*). One intraductal adenocarcinoma could not be resected and the histological diagnosis was established using intraoperative biopsy. One patient died in the postoperative period following total pancreatectomy. Thirteen of 18 intraductal

Table 2 Clinicopathological features of patients with intraductal tumour of the pancreas

	Hyperplasia ($n=4$)	Adenoma ($n=6$)	Adenocarcinoma ($n=18$)	Total ($n=28$)
Mean age (years)	62·8	63·9	65·1	64·5
Sex ratio (M : F)	3 : 1	6 : 0	15 : 3	24 : 4
Symptomatic	1	1	16	18
High serum CEA level	0 of 4	1 of 5	7 of 17	8 of 26
High serum CA19-9 level	0 of 4	0 of 5	7 of 17	7 of 26
Tumour size (cm)	1·7	2·9	5·4	4·4
Main pancreatic duct type	0	0	12	12
Enlarged orifice	0	1	15	16
MPD ≥ 5 mm	0	2	18	20
Malignant preop. cytology or histology	0 of 3	0 of 4	12 of 14	12 of 21
Macroscopic mural nodule	0	4	18	22

CA, carbohydrate antigen; CEA, carcinoembryonic antigen; MPD, main pancreatic duct

Table 3 Surgical treatment of cystic pancreatic tumours with mucin production

	n	PD	PPPD	DPPHR	DP	TP	Not resected
Intraductal tumour							
Hyperplasia	4			2	2		
Adenoma	6	1	2		3		
Adenocarcinoma	18	7	2		3	5	1
Mucinous cystic tumour							
Adenoma	4				4		
Adenocarcinoma	2				2		
Total	34	8	4	2	14	5	1

PD, pancreatoduodenectomy; PPPD, pylorus-preserving pancreatoduodenectomy; DPPHR, duodenum-preserving pancreatic head resection; DP, distal pancreatectomy; TP, total pancreatectomy

adenocarcinomas and all mucinous cystic adenocarcinomas were histologically confirmed to have been resected completely.

Among patients with intraductal adenocarcinoma the depth of invasion was *in situ* in six, confined to pancreatic stroma in three, and extended to the serosal surface or into peripancreatic tissue in nine. Two mucinous cystadenocarcinomas invaded the cyst wall stroma. Lymph node metastases were found in three patients with intraductal adenocarcinoma involving peripancreatic tissue.

Survival

All patients with benign tumours survived without evidence of recurrence. All five patients in whom carcinomas were incompletely resected or were irresectable died from cancer 2–21 months after operation. Four patients with intraductal adenocarcinomas died from other diseases. One patient with resectable intraductal papillary adenocarcinoma with regional nodal metastasis died from local recurrence and hepatic metastasis 32 months after resection. Eight patients with intraductal adenocarcinoma and two patients with mucinous cystic adenocarcinoma survived without evident recurrence at 2–10 years.

Discussion

The so-called mucin-producing pancreatic tumours, characterized by excessive mucin secretion from the dilated orifice of the ampulla of Vater, are often diagnosed based on clinical features[7–10]. In general, mucin-producing tumours are considered to be IDTs. On the other hand, several investigators have indicated that both IDTs and MCTs should be classified under the same category, and reported as mucin-producing tumours[11]. Therefore, in the present study, the term 'cystic pancreatic tumours with mucin production' was used, rather than 'mucin-producing pancreatic tumours', in order to avoid confusion. IDT has been given various names, including intraductal papillary neoplasm or tumour[3–5] and intraductal papillary mucinous neoplasm or tumour[12,13]. IDT, especially those tumours accompanied by dilatation of the main pancreatic duct, is synonymous with mucinous ductal ectasia[2,14], intraductal mucin-hypersecreting neoplasm[15,16] and mucin-hypersecreting tumour[17].

In the present study, cystic pancreatic tumours with mucin production were classified according to the classification of pancreatic carcinoma by the Japanese Pancreatic Society[1]. While this classification does not include hyperplasia, four cases of hyperplasia were included because this condition is sometimes considered to be a potent precursor of malignancy[18], and was often clinically difficult to differentiate from adenoma.

Clinical examination of patients with cystic pancreatic tumours with mucin production in the present study demonstrated differences between IDT and MCT with regard to age, sex and tumour location. Thus, most IDTs arose from the pancreatic head in elderly men, whereas MCTs were found in the body–tail in middle-aged women. These differences were similar to those described in previous reports[3–5]. Although it is often difficult to distinguish branch-type IDTs from MCTs by imaging procedures, it is essential to establish whether a cystic tumour represents dilated pancreatic ducts or a cyst with a thick fibrous capsule. Therefore, ERCP in patients with IDT can identify the presence of dilated pancreatic ducts. ERCP in patients with MCT can also show cysts that communicate with the main pancreatic duct, although the whole cavity cannot be visualized sufficiently because of the large size and abundant mucin.

As reported previously, mural nodules are often thought to be malignant in imaging studies for both IDT and MCT[5,10,19,20]. Recently, Fukushima *et al.*[4] measured the height of mural nodules on histological sections using a micrometer. They showed that no cases of hyperplasia presented as mural nodules, similar to the present results, and that the mean height of an intraductal adenoma, an intraductal adenocarcinoma, a mucinous cystadenoma, and two mucinous cystadenocarcinomas was 1·6, 5·3, 1·0 and 2·5 mm respectively. Furthermore, Yamaguchi *et al.*[19] also reported that the mean diameter of mural nodules was 5·1 mm in benign lesions and 20·5 mm in malignant lesions. Thus, the above results, together with those of the present study, indicate that the height and size of mural nodules measured by imaging procedures such as endoscopic

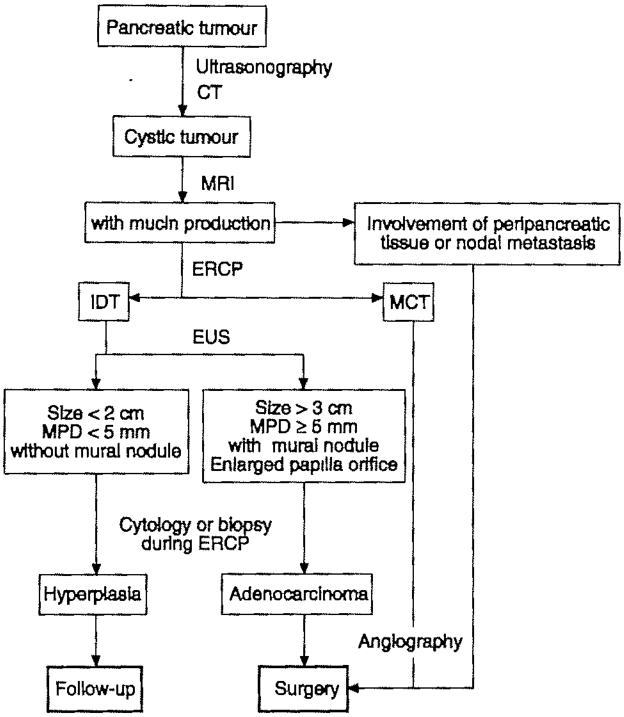

Fig. 5 Diagnosis and treatment strategies for cystic pancreatic tumours with mucin production. CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; IDT, intraductal tumour; MCT, mucinous cystic tumour; MPD, main pancreatic duct; MRI, magnetic resonance imaging

ultrasonography might be useful for the assessment of malignancy.

Several studies have characterized the clinical features of malignant IDT[5,10,19,20]. Obara *et al.*[20] reported that all IDTs larger than 4 cm were malignant, whereas branch duct-type IDTs smaller than 3 cm without dilatation of the main pancreatic duct or mural nodule were hyperplastic. Similarly, Kimura *et al.*[10] suggested that IDTs larger than 3 cm were mostly malignant. In the present study, the mean size of IDTs classified as hyperplasia, adenoma and adenocarcinoma was 1·7, 2·9 and 5·4 cm respectively. IDTs smaller than 2 cm without either mural nodules or dilatation of the main pancreatic duct were hyperplastic. On the other hand, IDTs larger than 3 cm with mural nodules, enlarged papilla orifice and dilatation of the main pancreatic duct were mostly carcinomas. Clinical symptoms, raised serum CEA and CA19-9 levels, and dilatation of the main pancreatic duct were found more often in patients with adenocarcinoma than in those with hyperplasia or a benign cyst. The present study did not include patients with chronic pancreatitis associated with intraductal hyperplasia and adenoma, in whom such pathology is frequently identified.

Preoperative diagnostic investigation cannot distinguish accurately between mucinous cystadenoma and mucinous cystadenocarcinoma[21]. Cytology of cyst fluid by percutaneous aspiration might show a high specificity; however, in the authors' institution, this test has not been performed lately because of concern related to the potential seeding of malignant cells during the procedure[2]. Cytological examination of the pancreatic juice, biopsy of the mural nodule and pancreatoscopy during ERCP could, however, provide useful information for differentiating malignant from benign tumours and avoid the risk of tumour seeding.

Obara *et al.*[22] reported five patients with IDT who showed no change in tumour size over a mean of 29 months. They also followed patients with hyperplasia in IDTs without surgical procedures and argued that such a management strategy might be an acceptable approach. During follow-up it is important to estimate the size of cystic tumour and dilatation of the main pancreatic duct frequently by ultrasonography and CT.

Intraductal adenomas and adenocarcinomas and MCTs require complete tumour excision. At present, the standard operation in the authors' institution for IDTs of the pancreatic head is pylorus-preserving pancreatoduodenectomy. As these tumours tend to spread in the pancreatic duct, frozen-section examination of the cut end of the pancreas should be performed during operation. Progression of the disease process in intraductal adenocarcinoma includes invasion of the pancreatic parenchyma as well as peripancreatic tissue. These advanced cases require extended pancreatectomy[23]. In this study, there were six patients with intraductal adenocarcinoma in which the depth of invasion was *in situ* without nodal metastasis. Operation for these *in situ* adenocarcinomas and adenomas may involve duodenum-preserving pancreatic head resection[24] or even partial pancreatic resection, whereas diagnostic procedures, including intraoperative frozen-section examination of the tumour, often do not reliably distinguish adenocarcinomas from adenomas. *Fig. 5* provides a summary of the authors' approach to the diagnosis and treatment of cystic pancreatic tumours with mucin production.

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Original article

Influence of a specialized leg ulcer service on management and outcome

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Background: The organization of leg ulcer care is poorly defined in the community. This study assessed the overall influence of a specialized community service on management and outcome of chronic leg ulcers, irrespective of aetiology.

Methods: Assessment and outcome of ulcers were compared in patient samples ($n = 200$) from East and West Gloucestershire, before and after the introduction of specialized clinics into East Gloucestershire. In clinics, vascular disease was routinely assessed by duplex scanning and determination of the ankle : brachial pressure index.

Results: There was no coordinated community structure for the care of patients with leg ulcers before the service was introduced, and 74 and 67 per cent of limbs in East and West Gloucestershire respectively had aetiology undiagnosed. After introduction of the clinics, the 12-week healing rate increased from 12 to 22 per cent in East Gloucestershire ($P = 0{\cdot}05$) and to 47 per cent in the specialized East Gloucestershire clinics ($P < 0{\cdot}001$). The 12-month recurrence rate decreased from 50 to 41 per cent in East Gloucestershire and to 17 per cent in the East clinics ($P < 0{\cdot}001$). The West Gloucestershire control showed no significant changes.

Conclusion: A specialized leg ulcer service with defined protocols provides an improved management structure for treating patients with leg ulcers in the community. Accurate diagnosis of chronic leg ulcers and improved outcome may be achieved within this specialized service.

Paper accepted 25 February 2000

British Journal of Surgery 2000, **87**, 1048–1056

Introduction

Chronic leg ulceration is a common and expensive problem[1–5]. Venous reflux is detectable in about 70 per cent of all leg ulcers but aetiology is often multifactorial[6–8]. Low healing and high recurrence rates in the community persist and are usually considered inevitable. The 12-week healing rate for venous leg ulcers after treatment in the community may be as low as 22 per cent and the 12-month recurrence rate as high as 69 per cent[9–12]. These poor outcomes may result from inaccurate diagnosis, lack of or inappropriate compression, and failure to identify patients with limbs that may benefit from surgery.

The recent introduction of community leg ulcer clinics has improved overall efficiency of management[13]. However, patients continue to be managed without investigation of the underlying pattern of venous abnormality and without any vascular surgical opinion[13]. It is fundamental that a modern leg ulcer service should incorporate non-invasive vascular assessment. This should be followed by safe management, including full compression therapy, modified compression therapy and consideration for appropriate surgical intervention[14–20].

In East Gloucestershire it has been shown previously that patients with ulcerated limbs may be practically and usefully investigated in a one-stop vascular assessment clinic[14,21]. Subsequently, venous leg ulcer healing and recurrence rates in East Gloucestershire were shown to have improved within a specialized leg ulcer service[15]. The present study assessed the overall impact of the service on patients with ulcerated limbs, irrespective of aetiology and place of treatment, and compared this with findings in a contemporaneous group of patients with ulcerated limbs from neighbouring West Gloucestershire.

Patients and methods

Study design

This was a two-centre, countywide, before and after study with a parallel control group. The intervention was the introduction of a coordinated, community-based, leg ulcer service led by vascular surgeons into East Gloucestershire that included the best current methods available for leg ulcer assessment and management[15]. The impact of this intervention was compared with that for existing and parallel control services in both East and West Gloucestershire, where leg ulcer care was deliberately unaffected by any change and allowed to progress naturally. *Fig. 1* illustrates the design of the study.

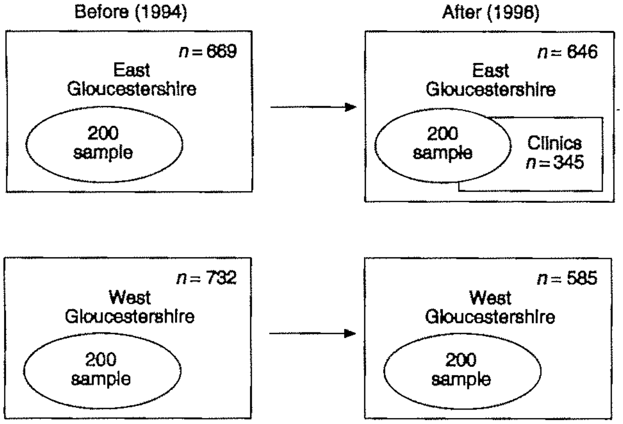


Fig. 1 Study design showing random samples of patients selected from East and West Gloucestershire leg ulcer populations before and after introduction of the specialized clinics (*n* = no. of patients with leg ulcer)

Baseline community audits (East and West Gloucestershire)

Demographic data including population, age and sex distribution across East and West Gloucestershire were collected. All patients treated for leg ulcers in the two regions during the 3 months from 1 July to 30 September 1994 inclusive were identified from a prospectively completed computer database, general practitioner records and practice/district nurse file records. Samples of 200 patients were randomly selected by means of RAND software (Microsoft, Redmond, Washington, USA). Ulcerated limbs from patient samples were included if the ulcers were of more than 4 weeks' duration and within the gaiter level (thereby excluding foot ulcers). The separation between limb and foot was made at a point 2·5 cm below the medial malleolus[8]. General practitioner and nursing records were reviewed to verify the presence of leg ulceration fulfilling these criteria. Prevalence estimates for chronic leg ulcers were estimated for this 3-month period on each side of the county using the following equation: prevalence = no. of patients with true leg ulcer in sample/200 × total no. patients/overall population.

Methods of ulcer assessment, 12-week healing and 1-year recurrence rates were recorded directly from information gathered from the treatment records.

Specialized community clinics in East Gloucestershire

In 1995 five community-based leg ulcer clinics were established in East Gloucestershire to which patients with leg ulcers were referred. Hospital practitioners, general practitioners, district and practice nurses were encouraged to refer all patients to the service. Two specialist leg ulcer nurses were involved in the service and their responsibilities included: (1) assessment of patients at the vascular laboratory along with a vascular technologist; (2) coordinating weekly attendance at the five community clinics; (3) bandaging and pinch-grafting leg ulcers; (4) providing easy access for education and advice for community nurses; and (5) liaison with the vascular surgical department.

Each limb was initially assessed for arterial disease using a hand-held Doppler ultrasonographic instrument (Huntleigh, Cardiff, UK) to measure the resting ankle : brachial pressure index (ABPI). Venous disease was assessed by venous duplex ultrasonography (HP Sonos 2000; Hewlett Packard, Massachusetts, USA) and significant reflux was defined as that occurring for more than 1 s following the release of manual calf compression[14,15,22]. Superficial venous insufficiency included reflux in the saphenofemoral and saphenopopliteal junctions, long and short saphenous veins, and perforating veins. Deep venous insufficiency included reflux in the common femoral, superficial femoral and popliteal veins.

Management in specialized community clinics in East Gloucestershire

Patients were seen weekly in the East Gloucestershire community clinics and four-layer graduated compression bandaging (Profore; Smith & Nephew, Hull, UK) was applied to limbs without arterial insufficiency (ABPI greater than 0·85 in normal vessels). Patients with superficial venous incompetence alone were offered venous surgery. This involved saphenofemoral and/or saphenopopliteal disconnection with stripping and avulsion. Incompetent perforating veins detected in the absence of deep venous insufficiency were localized before operation and ligated or avulsed through small incisions. Unusual ulcers or ulcers that failed to demonstrate healing at 12 weeks were biopsied to exclude malignancy. Ulcers with a clean base and that were more than 3 cm in diameter were pinch-skin grafted in the clinic by the specialist leg ulcer nurse under local anaesthesia using standard grafting techniques[23].

Mixed venous–arterial ulcers were managed according to the degree of ischaemia as estimated from the ABPI[24,25]. Mixed ulcers with moderate arterial disease (ABPI greater than 0·5 but less than or equal to 0·85) were treated with modified compression bandaging applied by a trained specialist vascular nurse[12]. During modified compression, ulcerated limbs were checked regularly for any adverse effects such as development of pain or a reduction in ABPI to 0·5 or less. Development of adverse effects at any stage, or failure to show signs of improvement after 3 months, prompted further investigation with arteriography and consideration for revascularization by angioplasty or bypass surgery. Patients with ulcerated limbs with severe mixed arterial–venous disease (ABPI of 10·5 or less) or purely arterial disease were offered early arteriography with a view to revascularization[16].

Healed non-ischaemic limbs were fitted with community grade class II below-knee compression stockings (Duomed; Medi, Hereford, UK). Patients were reviewed 1, 3, 6, 9 and 12 months after ulcer healing. All patients had open access to clinics if ulcers recurred. Malignant ulcers were treated by wide local excision. Other aetiologies such as diabetes mellitus and rheumatoid arthritis were assessed objectively by routine blood tests such as estimation of blood glucose levels and plasma viscosity, before any specialist intervention.

After introduction of specialized community clinics in East Gloucestershire

All patients treated for leg ulceration in both East and West Gloucestershire during the 3 months (from 1 September to 30 November 1996) after the introduction of specialized clinics in East Gloucestershire were identified using identical data collection methods to those used before the clinics were introduced. In East Gloucestershire patients may or may not have been treated in a specialized clinic. Clinical files were verified for ulcerated limbs fulfilling the inclusion criteria and the 12-week healing and 12-month recurrence rates were recorded. Additionally, all consecutive limbs managed in the specialized clinics were followed prospectively for similar healing and recurrence data.

Statistical analysis

All statistical analyses were performed on a personal computer using the SPSS for Windows Advanced Statistical Package (version 7.0; SPSS, Chicago, Illinois, USA). Healing and recurrence data were analysed by constructing Kaplan–Meier survival curves. Significant differences in outcome were determined with the log rank test.

Ethics

Ethical approval for the study was granted by the Gloucestershire Ethical Committee.

Results

Demographics

East Gloucestershire had a population of 215 289, with 39 371 persons older than 65 years (18 per cent); West Gloucestershire had a population of 319 211, with 51 164 persons aged over 65 years (16 per cent)[26]. East and West were well matched for age ($P = 0{\cdot}54$) and sex ($P = 0{\cdot}17$) distribution.

Prevalence of chronic leg ulceration in East and West Gloucestershire

The estimated prevalence of chronic leg ulceration in East Gloucestershire was 2·1 per 1000 population and in West Gloucestershire 1·5 per 1000.

Before introduction of the specialized clinic service in East Gloucestershire

In the groups of 200 community patients randomly selected from 669 patients identified in East Gloucestershire and 732 in West Gloucestershire, 154 and 141 ulcerated limbs respectively met the inclusion criteria.

After introduction of the specialized clinic service

In the groups of 200 patients randomly selected from 646 patients in East Gloucestershire and 585 in West Gloucestershire, 155 and 170 ulcerated limbs respectively met the inclusion criteria. Only 40 per cent of community leg ulcer patients were referred to the specialized service; 60 per cent continued treatment in the community despite encouragement to refer all patients[15].

Within the East Gloucestershire specialized clinic service

Consecutive limbs managed in the specialized community clinics over the first 2 years were selected for comparison.

The inclusion criterion for the present study for ulcerated limbs in the healing phase was the presence of an unhealed ulcer. Patients who refused to attend the clinics were excluded. A total of 339 limbs was entered into this part of the study; three were identified as having malignant disease.

The inclusion criterion for the present study for limbs in the recurrence phase was the presence of a healed ulcer that had healed either before or during treatment. Patients who refused to attend the clinics were excluded. Some 291 limbs were entered into this part of the study.

Assessment and aetiology

Of 154 limbs reviewed from East Gloucestershire before introduction of the specialized service, arterial insufficiency as judged by palpation of pulses was recorded in nine (6 per cent) and by hand-held Doppler ultrasonography in a further five (3 per cent). A diagnosis of ulceration was recorded in 40 (26 per cent) and included 35 (23 per cent) venous, four (3 per cent) arterial and one (1 per cent) mixed venous–arterial ulcer. Thus 114 (74 per cent) limbs remained undiagnosed during management.

Of 141 limbs reviewed from West Gloucestershire before the specialized service was introduced, arterial insufficiency as diagnosed by pulses was recorded in 12 (9 per cent) and by hand-held Doppler ultrasonography in a further nine (6 per cent). A diagnosis of ulceration was recorded in 47 (33 per cent) and included 44 (31 per cent) venous, one (1 per cent) arterial, one (1 per cent) mixed venous–arterial and one (1 per cent) malignant. Thus 94 (67 per cent) limbs remained undiagnosed during management.

No limbs in the 'before' groups had been assessed by plethysmography, venous duplex scanning or venography. *Table 1* summarizes the wide variety and combination of factors that may have been implicated in the cause of leg ulceration. All 336 limbs are listed after exclusion of the three (1 per cent) malignant ulcers.

Leg ulcer outcome

The 12-week healing and 1-year recurrence rates according to ulcer aetiology as determined by the one-stop assessment are also shown in *Table 1*. A total of 336 limbs is included in the healing group, excluding the three malignant ulcers. All 291 limbs are included in the recurrence group. *Table 1* summarizes the healing and recurrence rates within the service according to aetiology. The presence of arterial disease seemed to predispose to lower 12-week healing rates: 11 (19 per cent) of 57, two of 14, and none of three ulcers (*Table 1*). Limbs that were difficult to scan tended to predispose to lower healing rates (none of three ulcers, and two of seven ulcers) and higher 1-year recurrence rates (two of four ulcers). Limbs with no evidence of significant arterial or venous disease had a 12-week healing rate of 13 of 20 but a poor 1-year recurrence rate of seven of 20.

Healing

The 6- and 12-week healing rates before the specialized clinics were, respectively, 2 and 12 per cent in East Gloucestershire and 4 and 12 per cent in West Gloucestershire. After introduction of the specialized clinics, the 6- and 12-week healing rates were 8 and 22 per cent in East Gloucestershire ($P = 0{\cdot}05$) and 4 and 14 per cent in West Gloucestershire ($P = 0{\cdot}76$). In the specialized East Gloucestershire clinics alone, the respective healing rates were 24 and 48 per cent ($P < 0{\cdot}001$). *Figs 2* and *3* summarize the healing rates in the different groups by the Kaplan–Meier method. The 12-week healing rate of all ulcerated limbs in the absence of diabetes or rheumatoid arthritis ($n = 273$) was 51 per cent, compared with 30 per cent in those with diabetes and/or rheumatoid arthritis ($n = 63$) ($P < 0{\cdot}01$, log rank test).

Recurrence

Before the specialized clinics, ulcer recurrence rates at 6 and 12 months were, respectively, 43 and 50 per cent in East Gloucestershire and 35 and 48 per cent in West Gloucestershire. After introduction of the specialized East clinics, the 6- and 12-month recurrence rates were 39 and 41 per cent in East Gloucestershire ($P = 0{\cdot}65$) and 40 and 51 per cent in West Gloucestershire ($P = 0{\cdot}61$). In the specialized clinics alone, the 6- and 12-month recurrence rates were 13 and 17 per cent, respectively ($P < 0{\cdot}001$). *Figs 4* and *5* summarize the recurrence rates in the different groups by the Kaplan–Meier method. The 1-year recurrence rate of all healed limbs in the absence of diabetes or rheumatoid arthritis ($n = 257$) was 16 per cent, compared with ten (29 per cent) of 34 in those with diabetes and/or rheumatoid arthritis ($P = 0{\cdot}03$, log rank test).

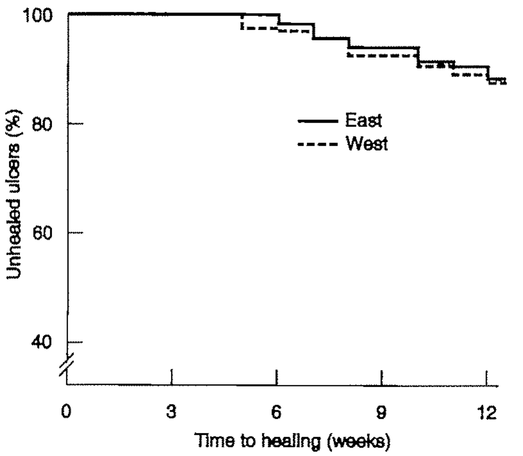
Discussion

Previous studies from Gloucestershire have confirmed the importance and practicality of one-stop, specialized, non-invasive vascular assessment in the management of patients with leg ulcers[14,21]. Ulcerated limbs suitable for venous surgery and mixed venous–arterial ulcers were readily identified, and management protocols and outcomes were assessed for these ulcers within the service[15,16]. The present study included East and West Gloucestershire regions, and suggests that the assessment and outcome of patients with chronic leg ulcers, irrespective of aetiology, may be

Table 1 Cumulative 12-week healing and 1-year recurrence rates for leg ulcers according to aetiological subgroup

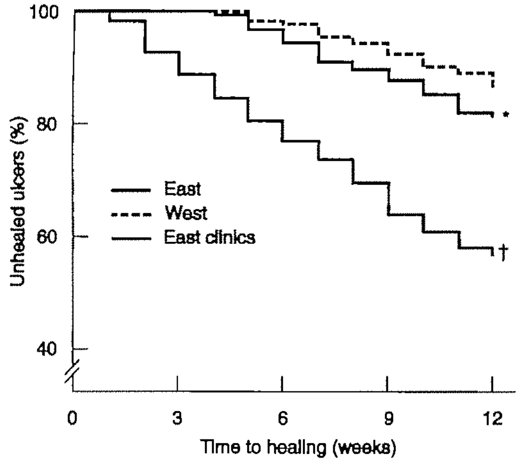
Aetiological subgroup*	Healing at 12 weeks	Recurrence at 1 year
Deep venous disease alone		
None	9 of 15	3 of 13
DM	0 of 0	0 of 0
RA	1 of 2	0 of 1
DM + RA	0 of 0	0 of 0
Total	10 of 17	3 of 14
Deep and superficial venous disease		
None	55 of 100 (55)	17 of 98 (20)
DM	4 of 9	1 of 9
RA	3 of 5	0 of 3
DM + RA	1 of 1	1 of 1
Total	63 of 115 (55)	19 of 111 (18)
Superficial venous disease alone with surgery		
None	34 of 60 (57)	4 of 59 (7)
DM	2 of 5	0 of 4
RA	4 of 7	1 of 5
DM + RA	0 of 0	0 of 0
Total	40 of 72 (56)	5 of 68 (8)
Superficial venous disease alone without surgery		
None	18 of 26	6 of 26
DM	0 of 2	1 of 4
RA	0 of 3	0 of 0
DM + RA	0 of 0	0 of 0
Total	18 of 32	7 of 30
Mixed venous and arterial disease		
None	11 of 46	2 of 37
DM	0 of 5	1 of 2
RA	0 of 6	0 of 0
DM + RA	0 of 0	0 of 0
Total	11 of 57 (19)	3 of 39
Arterial disease alone		
None	2 of 8	1 of 5
DM	0 of 5	0 of 0
RA	0 of 1	0 of 0
DM + RA	0 of 0	0 of 0
Total	2 of 14	1 of 5
Arterial disease with an inadequate venous scan		
None	0 of 0	0 of 0
DM	0 of 1	0 of 0
RA	0 of 2	0 of 0
DM + RA	0 of 0	0 of 0
Total	0 of 3	0 of 0
No arterial disease with an inadequate venous scan		
None	1 of 5	1 of 3
DM	1 of 1	1 of 1
RA	0 of 1	0 of 0
DM + RA	0 of 0	0 of 0
Total	2 of 7	2 of 4
Normal venous scan with no arterial disease		
None	10 of 13	3 of 16
DM	0 of 0	0 of 0
RA	3 of 6	4 of 4
DM + RA	0 of 1	0 of 0
Total	13 of 20	7 of 20
Total	159 of 336 (47)	50 of 291 (17)

Values in parentheses are percentages. *Vascular status was determined by duplex scanning and estimation of ankle : brachial pressure index. DM, diabetes mellitus; RA, rheumatoid arthritis



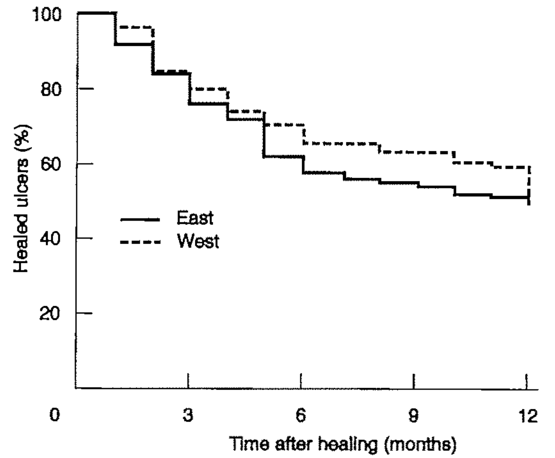
No. at risk					
East	154	154	151 (2)	142	136 (12)
West	141	141	136 (4)	130	124 (12)

Fig. 2 Healing rates of chronic leg ulcers in East and West Gloucestershire before introduction of the specialized service. Values in parentheses are cumulative healing rates



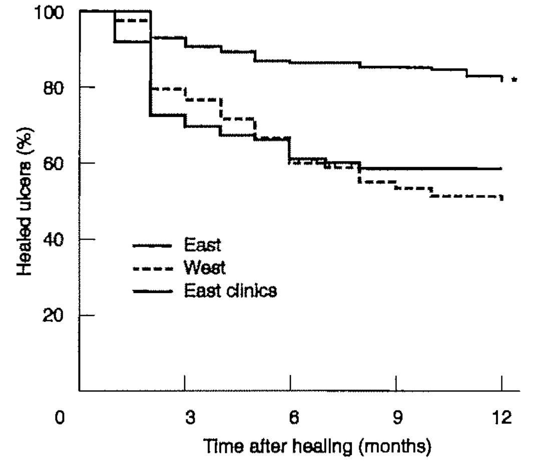
No. at risk					
West	170	170	163 (4)	156	147 (14)
East	155	155	143 (8)	134	121 (22)
East clinics	339	292	251 (25)	209	172 (47)

Fig. 3 Healing rates of chronic leg ulcers in East and West Gloucestershire after introduction of the specialized service. Values in parentheses are cumulative healing rates. *$P = 0{\cdot}05$, †$P = 0{\cdot}001$ *versus* West Gloucestershire (log rank test)



No. at risk					
East	114	84	63 (43)	56	53 (50)
West	86	65	54 (35)	50	42 (48)

Fig. 4 Recurrence rates of healed leg ulcers in East and West Gloucestershire before introduction of the specialized service. Values in parentheses are cumulative healing rates



No. at risk					
West	105	71	48 (40)	30	11 (51)
East	93	61	47 (39)	26	0 (41)
East clinics	291	248	222 (13)	189	154 (17)

Fig. 5 Recurrence rates of healed leg ulcers in East and West Gloucestershire after introduction of the specialized service. Values in parentheses are cumulative healing rates. $P = 0{\cdot}001$ *$P = 0{\cdot}001$ *versus* East and West Gloucestershire (log rank test)

improved by establishing a specialized, vascular surgeon-led, community-based, leg ulcer service. The majority of patients remain in the community while gaining access to specialized services[27].

Community clinics are an efficient and cost-effective means of managing patients with chronic leg ulcers[10,13], but the service introduced in East Gloucestershire was special as it was designed to include the best current methods available for management. These methods included venous duplex scanning, estimation of ABPI, four-layer compression, modified compression, and surgery where appropriate[14–20]. This complete service was unique in its combination of accurate vascular assessment and option for surgical management in a single unit. It was not the objective to evaluate each component of this service, but to assess the feasibility and impact of the complete package of care on all leg ulcers, irrespective of aetiology.

East and West Gloucestershire are neighbouring but geographically separate semirural communities with large populations affected by leg ulcer; they are served by different NHS Trusts within the same county health authority. It was thus possible to introduce a complete vascular-led leg ulcer service into East Gloucestershire while minimally influencing any changes in practice in West Gloucestershire, which was deliberately maintained as a parallel geographical control. All practitioners involved with leg ulcer care were made aware of the introduction of the specialized service and encouraged to refer all patients.

The fact that many patients were not referred introduces an element of selection bias within the study. Every attempt was made to educate practitioners through correspondence, and informal and formal talks to refer patients early, but these non-referral and non-attendance difficulties serve to highlight the problem of introducing any new service into a large area with firmly established practices. Practitioners sometimes referred only patients with very indolent ulcers, or those that were most mobile, or those with recurrence, or simply left it to the patient or nurse carer to decide. These are confounding factors within the study, but any large service introduced into a community would have such problems to some degree; this should not detract from an attempt to assess the overall influence of the new specialized service.

The pre-existing leg ulcer services in Gloucestershire were shown to be less than ideal, with no coordinated infrastructure. Underlying aetiology of leg ulceration was identified objectively in only 6 and 3 per cent of cases in West and East Gloucestershire, respectively, despite knowledge that the cause of ulceration is vital for safe management of ulcers in the community. Failure to make a formal diagnosis may contribute to low healing and high recurrence rates in the community[28].

The improvement in healing of leg ulcers of more than 1 month's duration compares favourably with that described in other studies[10,13]. This improvement was best seen in ulcers treated within the clinics, but it was also reflected in the random sample from the whole community in which patients not referred to the clinics were included. It has been suggested that patients with more difficult and indolent ulcers are more likely to be referred to specialized clinics. It appears that specialized assessment, appropriate management and follow-up is not replicated outside the specialist service, despite the presence of some trained community nurses. All district nurses in East Gloucestershire have spent at least 2 months in the specialized service environment to enhance their skills in ulcer management and to promote understanding of the importance of early referral. However, practice nurses have not been involved in this experience and so widespread education has not been achieved throughout the community. This may be a reason for some of the differences in outcome within and without the clinics.

Complex, mixed aetiologies are common in chronic leg ulcers, and treatments need to be tailored to individual requirements[6–8,21,29]. The use of high-compression bandaging makes it essential to exclude limbs with arterial insufficiency, for which high compression may precipitate critical ischaemia[30,31]. Mixed arterial–venous ulcers respond well to reduced compression therapy within a clearly defined protocol, but this requires meticulous assessment and a carefully coordinated surveillance programme to detect adverse effects[16].

In the present study, patterns of underlying venous disease did not seem to affect outcome, except after venous surgery which was shown to reduce early recurrence[15]. The addition of confounding diseases such as diabetes or rheumatoid arthritis also seemed to affect the overall outcome adversely. This emphasizes the importance of a complete knowledge of aetiology to predict resource requirements. Arterial disease was also confirmed as a factor that complicated ulcer management and delayed healing[16]. Limbs that were technically difficult to scan, usually due to size, oedema or immobility, had lower 12-week healing and higher 1-year recurrence rates. These limbs may have had a significant underlying problem, such as unrecognized venous insufficiency or severe muscle inactivity. Limbs with normal vascular assessment healed early but had a greater tendency to recurrence. This may also be a reflection of all the rheumatoid ulcers failing to remain healed in the first year.

Appropriate compression, venous and/or arterial surgery and pinch-skin grafting were all components of leg ulcer management in the specialized service. Each plays an important role in the overall benefits achieved, but this study did not set out to identify the degree of importance of each contributing factor within the overall organization. Skin grafting may improve healing rates while leaving recurrence rates unaffected, but many factors are involved in the success of grafting and 100 per cent pinch graft 'takes' are rarely achieved.

Duplex imaging in this study was well tolerated[14,15,21,32]. Lower limb swelling was not usually a technical problem and in fewer than 3 per cent of limbs was the duplex image difficult to interpret. These limbs often caused management difficulties and tended to do poorly. Specialized venous assessment has not always been considered necessary in patients unwilling to consent to or likely to benefit from surgery[13]. However, venous surgery was an important and significant factor in reducing recurrence in the present study and a high acceptance rate of 75 per cent was achieved for surgical intervention[15]. Routine determination of complex, multifactorial aetiology, including the various patterns of vascular disease, diabetes and rheumatoid arthritis, provides information that may predict prognosis and help resource allocation in patients with chronic leg ulcers[33,34].

A specialized community-based leg ulcer service, run primarily by a specialist leg ulcer nurse with a coordinated follow-up programme, represents an advance in community leg ulcer care that improves diagnosis and healing, and reduces recurrence. It is a natural progression from the usual single-visit assessment clinic and allows difficult chronic ulcers of mixed aetiology to be identified and treated appropriately.

Acknowledgements

The authors are grateful to the South-West Regional Research and Development Directorate, Smith & Nephew UK Ltd, Medi UK Ltd and East Gloucestershire NHS Trust for financial support. They thank all general practitioners, and practice and district nurses, in Gloucestershire for facilitating data collection.

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Original article

Effect of contralateral disease on duplex measurements of internal carotid artery stenosis

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Background: Duplex ultrasonography is increasingly used as the sole method of imaging before carotid endarterectomy. This study investigated the measured degree of stenosis in the contralateral carotid artery before and after operation.
Methods: Duplex-derived peak systolic velocity (PSV), end-diastolic velocity (EDV) and internal carotid artery/common carotid artery (ICA/CCA) velocity ratios were measured in the contralateral unoperated ICA before 131 consecutive unilateral endarterectomies and compared with preoperative angiographic findings. Three months later duplex scans were repeated to assess whether there had been any alteration in the severity of the stenosis in the contralateral unoperated artery.
Results: Bilateral ICA disease (greater than 50 per cent stenosis) was present in 50 patients (38 per cent). Three months after operation, ultrasonography of the 105 unoperated, patent, contralateral arteries showed a decrease in mean(s.d.) PSV (1·21(0·83) *versus* 1·07(0·69) m/s; $P < 0·01$) and EDV (0·41(0·29) *versus* 0·35(0·24) m/s; $P < 0·01$). This resulted in 14 (42 per cent) of 33 patients with contralateral disease being downgraded to a less severe category of stenosis. Use of the ICA/CCA velocity ratio prevented overestimation in eight of the 14 patients, while preoperative angiography correctly classified 13 of the 14 patients.
Conclusion: Bilateral carotid artery disease can cause overestimation of the severity of stenosis by duplex ultrasonography if absolute velocity is used as the main criterion.

Presented to a meeting of the Vascular Surgical Society, Hull, UK, 1998, and published in abstract form as *Br J Surg* 1999; **86**: 705
Paper accepted 24 February 2000

British Journal of Surgery 2000, **87**, 1057–1062

Introduction

Duplex ultrasonography is the most commonly used investigation for assessing the severity of carotid atherosclerosis, and is increasingly used as the sole investigation before carotid endarterectomy[1–4]. However, duplex ultrasonography is unable to identify carotid siphon stenoses and 'trickle' flow, and it cannot accurately detect stenosis if the carotid bifurcation is severely calcified. There is also evidence that duplex velocities are artificially high when there is severe bilateral disease, resulting in overestimation of stenosis compared with contrast angiography[5–9]. Unnecessary operations on carotid stenoses are rarely reported, but are ineffective and sometimes harmful[10].

This study assessed the effect of carotid endarterectomy on velocity measurements in the contralateral carotid artery. All patients had carotid angiography before operation, and both preoperative and postoperative duplex imaging.

Patients and methods

Between December 1992 and April 1998, 131 consecutive patients underwent unilateral carotid endarterectomy for internal carotid artery stenosis. Some 117 patients had symptoms appropriate to the stenosis, eight were in the surgical arm of the Asymptomatic Carotid Surgery Trial[11], and six had endarterectomy for bilateral symptomless disease before coronary artery revascularization.

Preoperative bilateral duplex ultrasonography and contrast arteriography were performed in all patients.

Duplex imaging technique

Ultrasound scans were performed the day before operation and repeated 3 months later, or sooner if the patient developed neurological symptoms. An Acuson XP10 128 colour scanner (Mountain View, California, USA) was used

Table 1 Grading of carotid stenosis according to peak systolic and end-diastolic velocities (modified from Zierler and Strandness[12])

Peak systolic velocity (m/s)	Peak end-diastolic velocity (m/s)	Estimated stenosis (%)
< 1·25	< 0·50	< 50
> 1·25	< 0·60	50–59
> 1·25	> 0·60	60–79
> 1·25	> 1·0	80–99
No flow		Occlusion

with a high frequency (7·5 MHz) transducer, keeping the incident angle at less than 60°. Measurements of both peak systolic velocity (PSV) and peak end-diastolic velocity (EDV) were recorded at the narrowest point in the artery, and more proximal and distal readings were taken in the common carotid artery (CCA) and internal carotid artery (ICA). The estimated degree of stenosis was based on velocity criteria originally reported by Zierler and Strandness[12] with the 50–79 per cent category modified in the authors' laboratory into clinically relevant subdivisions (*Table 1*) and validated against angiographic findings. Stenoses were also categorized according to the ICA/CCA velocity ratio[13] (*Table 2*).

The intraobserver variation of carotid duplex imaging in this laboratory has been determined by repeating ultrasonography within 1 month on ten normal subjects and 30 patients with varying degrees of clinically stable carotid disease. This has been expressed as the repeatability, and was 0·24 and 0·12 m/s for peak PSV and peak EDV respectively[14].

Systemic blood pressure and pulse rate were recorded at the time of ultrasonography, and compared according to whether patients had unilateral or bilateral internal carotid artery stenosis greater than 50 per cent.

Arteriography

Intravenous digital subtraction arteriography was performed between 1 day and 6 weeks before operation. A 5-Fr catheter was passed via an antecubital vein into the superior vena cava and four boluses of 36 ml Ultravist 370 (Schering Health Care, Burgess Hill, UK) were pump-injected with imaging of two frames per second in anteroposterior and oblique planes. In 12 patients further definition was required with an arch arteriogram performed using a 5-Fr pigtail catheter via the femoral artery. Stenoses were graded according to the North American criteria using the ratio of the residual bulb diameter with respect to the normal distal ICA[15], and this measurement was used as the basis for surgical intervention.

Table 2 Grading of carotid stenosis according to systolic and end-diastolic internal/common carotid artery velocity ratios[13]

Peak systolic velocity ratio	Peak end-diastolic velocity ratio	Estimated stenosis (%)
< 1·8	< 2·6	< 60
> 1·8	> 2·6	60–79
> 3·7	> 5·5	80–99
No flow		Occlusion

Surgery

Carotid endarterectomy was performed under general anaesthesia with universal shunting. Before April 1997 the endarterectomy was closed primarily (99 procedures) but after this all patients had a 'patch' closure 27 with Dacron (Du Pont, Stevenage, UK) and two with long saphenous vein). Three patients had segmental carotid resection and bypass (two with the long saphenous vein and one with polytetrafluorethylene (PTFE)) for recurrent stenoses. Peroperative completion ultrasonography and arteriography was performed in all patients with immediate re-exploration and correction of any abnormality detected.

Statistical analysis

Changes in absolute velocities and velocity ratios in the contralateral unoperated side were compared with the paired *t* test. The preoperative severity of stenosis estimated by ultrasonography was compared with angiographic findings, as well as postoperative ultrasonography using kappa (κ) analysis (Clinstat; Prof. J.M. Bland, Department of Medical Statistics, St. George's Hospital Medical School, London, UK).

Results

Eighty-one of the patients were men (median age 64 (range 37–81) years) and 50 were women (median age 68 (range 45–85) years). Three of the 131 patients died within 30 days of operation (two had myocardial infarction and one an embolic stroke from a prosthetic cardiac valve); a further two patients died during the subsequent 2 months (one from a ruptured aortic aneurysm and the other from a cerebral haemorrhage). Two further patients had a postoperative stroke after primary closure, but no patient had a stroke following the introduction of routine patch angioplasty.

Preoperative imaging

The distribution of contralateral disease as assessed by duplex imaging and angiography is shown in *Table 3*.

Contralateral disease of between 50 and 99 per cent stenosis was reported in 33 (25 per cent) angiograms and in 35 (27 per cent) of the duplex scans. Fifteen patients (11 per cent) had a contralateral occlusion demonstrated on both investigations. Duplex imaging and angiography gave the same category of stenosis in 101 patients (77 per cent). When arteriography was used as the denominator, duplex imaging overestimated disease in 16 patients (12 per cent) and underestimated disease in 14 (11 per cent).

Postoperative haemodynamic changes

Mean systemic blood pressure and pulse rate in the patients with unilateral disease were noted to be 150/80 mmHg and 75 beats/min respectively before operation and 140/82 mmHg and 77 beats/min 3 months after operation (*P* not significant). In the patients with bilateral disease, blood pressure and pulse rate were 128/77 mmHg and 72 beats/min respectively before operation and 136/70 mmHg and 77 beats/min 3 months afterwards (*P* not significant).

At 3 months after endarterectomy six patients were noted to have significant recurrent disease at the endarterectomy site (four occlusions and two patients with 80–99 per cent restenosis). Of the four patients with a carotid occlusion one had an episode of amaurosis fugax and another had a completed stroke.

Table 3 Comparison of preoperative duplex ultrasonography and digital subtraction angiography of the unoperated internal carotid artery ($n = 131$)

Preoperative duplex imaging*	Degree of stenosis estimated by preoperative angiography (%) <50	50–59	60–79	80–99	100
Degree of stenosis (%)					
<50	73	4	4	0	0
50–59	8	2	3	1	0
60–79	0	2	6	2	0
80–99	2	0	4	5	0
100	0	0	0	0	15

$\kappa = 0{\cdot}60$ (0·48–0·73); $P < 0{\cdot}01$

Contralateral unoperated carotid artery

To assess whether successful endarterectomy reduced duplex velocities in the unoperated side, the following 26 patients were excluded from subsequent analysis: 15 patients with preoperative contralateral occlusion, the six patients with ipsilateral restenosis which would have undermined the haemodynamic improvement of the procedure, and the five who died before the 3-month postoperative scan.

The peak systolic and diastolic ICA velocities, and the ICA/CCA velocity ratios of the contralateral unoperated side are shown in *Table 4*. These were taken before operation and 3 months after the 105 endarterectomies. *Tables 5* and *6* show similar information in the patients whose preoperative contralateral disease was reported by duplex imaging to show stenosis greater than 50 and 80 per cent respectively. Both absolute velocity and velocity ratios were progressively higher in the groups with more severe contralateral disease. There was a significant decrease in velocity measurements 3 months after contralateral endarterectomy, with the mean PSV falling by 0·31 m/s (or 11 per cent; $P < 0{\cdot}01$) where the stenosis was reported to be greater than 50 per cent, and by 0·72 m/s (or 23 per cent; $P = 0{\cdot}01$) where the stenosis was reported to be greater than 80 per cent. Although there was also a decrease in ICA/CCA velocity ratio following contralateral surgery, this was not as consistent as the absolute velocity changes.

Table 7 shows how the changes in duplex velocity following contralateral endarterectomy translated into the classification of disease according to the modified Strandness criteria. Thirty-three patients had a preoperative duplex scan that suggested stenosis greater than 50 per cent. Fourteen (42 per cent) of these were reclassified to a lesser category following successful contralateral endarterectomy. This effect was most marked in the nine patients

Table 4 Changes in internal carotid artery peak velocities before and 3 months after contralateral endarterectomy ($n = 105$)

	Preop.*	3 months postop.*	Mean change (%)†	*P*
Systolic velocity (m/s)	1·21(0·83)	1·07(0·69)	−7 (−11 to −3)	<0·01
Diastolic velocity (m/s)	0·41(0·29)	0·35(0·24)	−4 (−12 to +4)	<0·01
Systolic velocity ratio	1·84(1·54)	1·59(1·21)	−2 (−9 to +5)	0·01
Diastolic velocity ratio	2·13(1·78)	2·05(1·64)	10 (0–20)	0·32

*Values are mean(s.d.); †values in parentheses are confidence intervals

Table 5 Changes in internal carotid artery peak velocities before and 3 months after contralateral endarterectomy in patients with ipsilateral stenosis greater than 50 per cent ($n = 33$)

	Preop.*	3 months postop.*	Mean change (%)†	*P*
Systolic velocity (m/s)	2·15(0·89)	1·84(0·74)	−11 (−19 to −3)	<0·01
Diastolic velocity (m/s)	0·72(0·33)	0·60(0·29)	−13 (−22 to −4)	<0·01
Systolic velocity ratio	3·24(2·08)	2·64(1·68)	−9 (−26 to +8)	0·02
Diastolic velocity ratio	3·79(2·34)	3·42(2·31)	−3 (−17 to +11)	0·10

*Values are mean(s.d.); †values in parentheses are confidence intervals

Table 6 Changes in internal carotid artery peak velocities before and 3 months after contralateral endarterectomy in patients with ipsilateral stenosis greater than 80 per cent ($n = 9$)

	Preop.*	3 months postop.*	Mean change (%)†	*P*
Systolic velocity (m/s)	3·21(0·68)	2·49(0·88)	−23 (−40 to +6)	0·01
Diastolic velocity (m/s)	1·17(0·23)	0·81(0·42)	−33 (−51 to −15)	<0·01
Systolic velocity ratio	4·85(2·53)	4·33(2·17)	13 (64 to −38)	0·48
Diastolic velocity ratio	5·97(3·21)	5·50(3·36)	−6 (−21 to +9)	0·33

*Values are mean(s.d.); †values in parentheses are confidence intervals

deemed to have severe (80–99 per cent) stenosis before operation; six of these patients were downgraded, two of whom had postoperative velocities suggestive of only mild (50–59 per cent) disease. In these 14 patients preoperative arteriography had correctly predicted the true severity of disease in 13 cases and also demonstrated that all had both vertebral arteries patent, with only one patient showing retrograde flow. There were no significant blood pressure changes in this group over the study interval, but review of the preoperative B-mode ultrasound scans showed calcification in three and complex plaque or intimal thickening in four patients.

Table 7 Changes in internal carotid artery stenosis assessed by duplex ultrasonography before and 3 months after contralateral endarterectomy ($n = 105$)

	Stenosis at 3 months (%)			
	<50	50–59	60–79	80–99
Preoperative stenosis (%)				
<50	71	0	1	0
50–59	5	7	2	0
60–79	0	3	7	0
80–99	0	2	4	3

$\kappa = 0{\cdot}66$ (0·52–0·81); $P < 0{\cdot}01$

Discussion

Contrast arteriography has been used to estimate the degree of carotid stenosis in the major trials of carotid endarterectomy[15,16]. However, some investigators advocate that duplex ultrasonography alone is required before carotid surgery[1–4]. In a survey of nearly 700 carotid endarterectomies performed in the UK and Ireland in 1994, approximately 45 per cent were completed without preoperative arteriography[17]. Ultrasonography does not assess the presence of proximal (aortic arch) or distal (carotid siphon) lesions, intracerebral vascular abnormalities, 'trickle flow' beyond a subocclusive arterial stenosis, and disease within heavily calcified vessels. There is also a tendency for standard duplex velocity criteria to overestimate the severity of stenosis when it is compared with arteriography using the North American criteria[5–9]. Hayes *et al.*[5] have demonstrated that this overestimation appears to be proportional to the severity of contralateral disease, with only 2·6 per cent of carotid stenoses being overestimated if contralateral stenosis is less than 45 per cent, and 35 per cent of scans being erroneously upgraded if there is a contralateral occlusion. These discrepancies are unlikely to be the result of observer variation as duplex underestimation of disease is relatively infrequent. Spadone *et al.*[6] have suggested that more reliance should be placed on the B-mode images whenever there is contralateral disease. However, of the 14 patients in whom the stenosis was reclassified following contralateral endarterectomy, seven had suboptimal ultrasound imaging as a consequence of mural calcification or complex plaque formation.

Attempts have been made to correct for overestimation of disease by altering the velocity thresholds for categories of stenosis. Hayes *et al.*[5] found that increasing the peak systolic frequency threshold for 45 per cent stenosis from 5·5 to 8·5 MHz in the presence of contralateral occlusion increased accuracy from 76 to 92 per cent. Fujitani *et al.*[7] reported that increasing peak systolic and end-diastolic frequency thresholds for 50 and 80 per cent stenoses by only 0·5 kHz, to 4·5 and 5·5 kHz respectively, reduced overestimation from 30 per cent to 6 per cent of their 154 patients with contralateral occlusion. Evaluating Fujitani *et al.*'s criteria prospectively, AbuRahma *et al.*[8] confirmed the low rate (4·4 per cent) of duplex overestimation of disease in the presence of a severe (greater than 80 per cent) contralateral stenosis, but noted underestimation in 29 per cent of the scans, suggesting that these criteria were unduly strict. By omitting the change in the end-diastolic frequency threshold, AbuRahma *et al.* reduced underestimation to only 2 per cent of scans, without increasing overestimation.

One of the inherent problems with these studies is that although arteriography is assumed to be the 'gold standard' there is still debate as to the best technique for measuring the stenosis on arteriography; the North American criteria tend to produce lower values[18]. To avoid the uncertainty introduced by comparison with arteriography, duplex imaging can simply be repeated following successful unilateral endarterectomy. Although an increase in velocity might be expected due to progression of disease, Bussutil *et al.*[9] noted a significant decrease in both the PSV and EDV after contralateral endarterectomy in 85 patients, with a decrease of at least one disease category in 44 (52 per cent). They did not clarify whether velocity decreases were related to the severity of contralateral disease or whether they were corrected by use of the ICA/CCA velocity ratio. Their study also failed to report whether changes in the disease category would have been clinically relevant.

The present study confirms a decrease in peak systolic and end-diastolic velocities on the unoperated side, which appears to be related to the severity of disease on that side and is not wholly corrected by expression of the velocity as a ratio of the more proximal velocity. These changes are clinically relevant; six of the nine patients reported to have 80–99 per cent stenosis were reclassified to a lower category following contralateral surgery. Without preoperative arteriography or repeat ultrasonography these patients could have been offered an inappropriate endarterectomy. More importantly, the velocity in the original operated artery was probably similarly increased by disease in the contralateral artery.

The increase in ultrasound velocity in the contralateral artery may be a consequence of increased collateral flow through it, producing a jet effect and artificially high velocities. Successful ipsilateral endarterectomy would lead to a reduction in collateral flow and more accurate velocity measurement. This hypothesis is supported by van Everdingen *et al.*'s study[19], which demonstrated that distal ICA PSV was related to ICA flow measured by magnetic resonance angiography (MRA). In this study patients with ICA flow in excess of 274 ml/min on MRA were more than twice as likely to have duplex overestimation of disease than those with smaller volume flows (46 *versus* 20 per cent). The extent of the discrepancy between serial ultrasonography before and after contralateral endarterectomy presumably reflects the proportion of blood passing through the imaged artery. It is possible that, where velocity changes are minimal, there are adequate ipsilateral periorbital and/or posterior circulatory collaterals; this is currently under investigation with MRA assessment of the circle of Willis.

In conclusion, the decrease in duplex-derived velocity measurements following successful contralateral endarterectomy is not wholly corrected by the use of velocity ratios and often leads to reclassification of the severity of disease. If the magnitude of this discrepancy is determined by the pattern of collateral flow, simple modification of velocity thresholds is unlikely to resolve the problem, and would in any case need to be audited by individual laboratories. Supplementary imaging is required if bilateral carotid artery disease is detected on duplex ultrasonography in a patient being considered for intervention.

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Original article

Role of a defunctioning stoma in the management of large bowel Crohn's disease

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Background: The faecal stream plays a significant role in the pathogenesis of Crohn's disease. This retrospective study aimed to assess the effect of faecal diversion on the natural history of refractory Crohn's colitis (RCC) and severe perianal disease (PAD).
Methods: All patients undergoing a defunctioning stoma without resection for RCC or PAD between 1970 and 1997 were studied. Indications for surgery, acute clinical response, subsequent outcome and stoma rates were recorded.
Results: Some 73 patients underwent a defunctioning stoma (55 RCC and 18 PAD). Acute remission was achieved in 63 patients (48 RCC, 15 PAD). Twenty-nine patients had subsequent closure of the defunctioning stoma (25 of 48 acute responders with RCC and four of 15 acute responders with PAD). Eleven patients with RCC and two with PAD achieved good long-term function without disease relapse (median follow-up 36 months). Overall 52 patients have undergone proctocolectomy or remain with a defunctioning stoma (37 with RCC and 15 with PAD).
Conclusion: Faecal diversion is associated with acute clinical remission in the majority of patients with RCC and PAD, but sustained benefit occurs less often. For selected patients, diversionary surgery alone offers a realistic alternative to major bowel resection.

Presented to the Annual Meeting of the Association of Coloproctology of Great Britain and Ireland, Southport, UK, June 1999 and published in abstract form as *Colorectal Disease* 1999; 1(Suppl 1): 4–5
Paper accepted 3 February 2000
British Journal of Surgery 2000, 87, 1063–1066

Introduction

The faecal stream plays a significant role in the pathogenesis of Crohn's disease[1]. In the 1960s Truelove *et al.*[2] and Oberhelman *et al.*[3] documented the beneficial effects of faecal diversion in the management of Crohn's colitis but subsequent publications debated its long-term value[4–6]. Zelas and Jagelman[6] and Burman *et al.*[5] reported high initial response rates to diversion (91 and 95 per cent respectively) but focused on high relapse rates (33 and 52 per cent) and low rates of restoration of bowel continuity (4 and 17 per cent). The benefit of faecal diversion to the debilitated patient was improved performance status, allowing definitive surgery to be performed later at less risk[6].

In 1983 Harper *et al.*[7] demonstrated the benefit of faecal diversion alone, or in combination with intestinal resection, for patients with Crohn's colitis. High rates of restoration of bowel continuity were achieved (61 of 102 patients) with 43 per cent of patients achieving closure without relapse. Contrary to earlier reports, they also noted a good initial response in patients with perianal Crohn's disease, including those with rectovaginal fistula[8].

The inconsistency in outcomes following faecal diversion for colorectal and perianal Crohn's disease still causes debate. Over the past two decades progress in the medical management of Crohn's disease and use of conservative surgical techniques may have affected the outcome of diversionary surgery in such patients. The aim of this report was to assess the role of faecal diversion alone on short-term remission and longer-term outcomes in patients with both refractory Crohn's colitis (RCC) and perianal disease (PAD).

Patients and methods

All patients with Crohn's disease who had undergone a defunctioning stoma between 1970 and 1997 were identified from the gastroenterology and stoma care databases.

Seventy-three patients underwent faecal diversion alone and form the basis of this study. Of these 73 patients, only 14 were part of Harper's original series[7]. Two patients, who eventually came to proctocolectomy, were subsequently diagnosed as having ulcerative colitis and indeterminate colitis. They were included in the analysis as they were believed to have Crohn's disease at the time of surgery. A further 40 patients were identified from the database in whom a defunctioning stoma had been used. In all 40, partial or extensive bowel resection was performed at the time of defunctioning for severe segmental disease, stricturing, perforation or aggressive pancolitis. All were excluded from the study in order to assess accurately the effect of diversion alone on RCC and PAD.

The following data were recorded: (1) indications for defunctioning surgery; (2) type of surgery; (3) early clinical response, assessed at 3 months after operation at outpatient review and defined as a reduction or cessation of gastrointestinal symptoms, a decrease in steroid or other medication and an improvement in general well being; (4) date of closure of stoma; (5) sustained response to closure of stoma; and (6) date of proctocolectomy.

Results

Seventy-three patients were reviewed, 40 women and 33 men of median age 40 (range 19–87) years. Fifty-five patients underwent faecal diversion for Crohn's colitis resistant to medical therapy. Eighteen of these had coexisting small bowel disease and 14 developed or had had minor perianal complications. All patients were taking corticosteroids or a combination of steroids, immunosuppressive agents (azathioprine, methotrexate) and 5-aminosalicylates (sulphosalazine, mesalazine) at the time of surgery. Thirty-eight underwent a split ileostomy, 16 a loop ileostomy and one a loop colostomy.

Eighteen patients had a defunctioning stoma for PAD alone. All had a combination of complex fistulas and perianal sepsis. Six women had an anovaginal or rectovaginal fistula and one man had a rectovesical fistula. One patient had an associated anal stenosis. All patients had persistent disease despite medical therapy and minor surgical procedures including insertion of setons to drain sepsis. Two patients had coexisting small bowel disease, four had coexisting small and large bowel disease, and 12 patients had coexisting rectal or colonic disease. Ten patients underwent a split ileostomy, four a loop ileostomy and four a colostomy.

Median time between onset of disease and diversionary surgery for both RCC and PAD was 48 (mean 66·4, range 1–360) months. Median follow-up after diversion (all 73 patients) was 36 (mean 54·4, range 2–204) months.

Three patients (4 per cent) included in the study died, one within 30 days of stoma formation and one within 30 days of reoperation for a parastomal hernia, 12 months after diversion. These deaths were due, respectively, to a colonic haemorrhage in a Jehovah's Witness who refused transfusion and a myocardial infarction in a patient with known ischaemic heart disease. The third death was cardiovascular and occurred 3 years after diversionary surgery. One other patient developed a parastomal hernia requiring operative revision. There were no other stoma-specific complications that required reoperation.

Short-term outcome

Early clinical remission was achieved in 63 of 73 patients. This was similar in both groups (*Table 1*). Restoration of intestinal continuity was achieved in 25 of the 48 patients with RCC who responded initially, compared with four of 15 with PAD. Median time to stoma closure was 12 (range 5–86) months.

Long-term outcome

The long-term outcome for both groups is summarized in *Table 1*. Overall, stoma closure with no subsequent relapse and good function was achieved in 11 of the 55 patients with colitis and in two of the 18 patients with PAD (median follow-up for acute responders 36 (mean 60·5, range 3–204) months. Segmental resection was performed at the time of closure in one patient for disease in the transverse colon. Proctocolectomy rates were similar in

Table 1 Outcomes

	Crohn's colitis ($n=55$)	Perianal Crohn's ($n=18$)
Acute remission	48 (87)	15 (83)
No remission	7 (13)*	3 (17)
Closure	25 of 48	4 of 15
Good outcome	11	2
Repeat diversion	3	1
Relapse	6	1
Proctocolectomy	4	0
Undecided	1	0
No closure	23 of 48	11 of 15
Ongoing stoma remission	5	4
Ongoing stoma (choice)	4	0
Relapse	1	0
Proctocolectomy	12†	6
Death	1‡	1‡

Values in parentheses are percentages. *Includes one death; †one patient elected to undergo proctocolectomy; ‡both patients had an ongoing stoma and were in remission

Table 2 Comparison of operative procedures

	Split ($n = 48$)	Loop ($n = 20$)
Overall closure with good outcome	7 (15)	7 (35)
Long-term stoma	38 (79)	11 (55)
Overall stoma avoidance	10 (21)	9 (45)
Overall proctocolectomy	26 (54)	5 (25)

Values in parentheses are percentages

patients with RCC and PAD. A permanent stoma was avoided in 18 of 55 patients with RCC compared with three of 18 with PAD.

Among the 34 patients who relapsed (excluding the ten non-responders), median time to relapse after diversion was 13 (range 3·5–176) months. Four patients relapsed in the first 6 months after diversion, 11 patients in the second 6 months and seven in the third 6 months. The 65 per cent of patients who relapsed did so in the first 18 months after diversion. Over 45 per cent of patients who relapsed after stoma closure did so within 3 months of restoration of intestinal continuity. Five patients in the colitis group expressed a preference for a stoma.

When operative procedures were compared (*Table 2*), closure with a good outcome was achieved in seven of 48 patients with a split ileostomy and seven of 20 with a loop stoma. Long-term stomas were less common after split compared with loop ileostomy. The proctocolectomy rate was higher in the split ileostomy group.

Discussion

Over the past two decades, in addition to steroids and 5ASA compounds, azathioprine and methotrexate have been validated in clinical trials for use in Crohn's colitis[9,10]. In patients with PAD the use of seton drainage, long-term antibiotics and cyclosporin for refractory fistulas are treatment options[11–14]. In patients with PAD, improved imaging of the adjacent tissues with magnetic resonance imaging[15] has permitted a more rational approach to therapy. Most recently the use of a chimeric monoclonal antibody to tumour necrosis factor α has been described to enhance healing of fistulas in Crohn's disease, including anal fistula[16].

However for a small number of patients, more definitive surgery remains the only treatment option. Over the 27 years studied in this present series, the mean number of simple diversionary procedures was 2·8 per year. The mean number of operations for Crohn's disease in this unit falls between 70 and 80 per year. This highlights that diversionary surgery alone is appropriate in only a small number of highly selected cases. For all patients studied, the only other surgical options would have been proctocolectomy or extensive bowel resection. Recent studies have shown that 28–31 per cent of all patients with colorectal Crohn's disease will come to permanent ileostomy[17,18] making the chance of salvage from a permanent stoma an important potential benefit of faecal diversion.

Restoration of bowel continuity was possible in 25 of 48 patients with Crohn's colitis. This is considerably higher than in the most recently published series where only four of 32 patients had bowel continuity restored[19]. Furthermore, 20 per cent of patients with Crohn's colitis had a relapse-free outcome following restoration of bowel continuity and 33 per cent avoided a long-term stoma. These outcomes are again better than might have been expected based on previously published literature and are based on large patient numbers[5,6,19]. The outcome was less good for patients with PAD. Only two of 18 patients achieved restored continuity with a relapse-free outcome and only three of 18 remained stoma free. Poorer closure rates for PAD are not surprising given the proportion of patients in this group with rectovaginal fistula and the unsatisfactory outcomes associated with such fistulas in Crohn's disease[20].

Attempts have been made to predict outcome following restoration of bowel continuity by faecal challenge into the defunctioned bowel[21]. No parameter, including faecal challenge, has been demonstrated to be predictive of outcome. The decision to close a temporary stoma is subjective, and based on careful clinical assessment of the patient and exclusion of stricturing and inflammation.

Despite more aggressive conservative strategies over recent decades, these data demonstrate that faecal diversion alone can still promote early clinical remission in 86 per cent of patients. The improvement in patient performance status in such patients has already been documented[6], and the benefits of delaying definitive and higher risk surgery are obvious. This study's remission rate at 3 months compares with that in a more recent study by Winslet *et al.*[19].

In the earlier part of this study a split ileostomy was the favoured method of faecal diversion. More recently a loop ileostomy, fashioned through a trephine incision with or without laparoscopy, has become the preferred approach. This avoids a laparotomy incision and has been shown to achieve almost complete defunctioning[22]. The retrospective comparison of operative techniques should be viewed cautiously. Over twice as many operations were performed in the split ileostomy group, and there were more patients with severe or complex disease in this group. A prospective, disease-stratified, randomized clinical trial would be necessary to clarify this issue.

The relevance of diversion colitis to outcome in this and other studies and the risk of neoplasia in the defunctioned segment are not known. Histological differentiation between quiescent Crohn's colitis and diversion proctocolitis can be difficult on mucosal biopsy and may confuse histological assessment of disease activity[23].

The issues of patient preference and the psychological impact of diversionary surgery need to be addressed. The benefits of a 'time buying', conservative operation over proctocolectomy in a high-risk patient group has already been noted[6]. It is arguable that a temporary ileostomy offers a less daunting psychological prospect, and allows time for appropriate counselling and acceptance of a lifelong stoma.

In conclusion, faecal diversion alone offers a positive alternative to extensive resection or proctocolectomy for a small group of selected patients. With more advanced treatments for Crohn's disease on the medical horizon, the preservation of bowel in the younger population should be a priority and may allow more successful restoration of bowel continuity in the future.

Acknowledgements

Dr C. M. Edwards is a Medical Research Council Training Fellow.

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Original article

Bascom's operation in the day-surgical management of symptomatic pilonidal sinus

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Background: Many treatments for symptomatic pilonidal sinus disease have been described. Ambulatory treatment with minimal morbidity and a rapid return to normal activity is desirable. Bascom's operation fulfils these requirements. This paper describes the operative technique and results of treatment.

Methods: Some 218 patients of mean age 27 years were treated as day cases. The mean duration of symptoms was 2·4 years. Sixty-eight per cent of patients had complex disease with more than two midline pits and/or a lateral discharging sinus. One hundred and eighty-three patients (84 per cent) were operated on under local anaesthesia.

Results: Ninety-five per cent of patients have been followed up for a mean of 12·1 (range 1–60) months. All except one midline wound healed. Lateral wounds healed after a mean of 4·0 (range 1–15) weeks. Postoperative complications were few, including bleeding in 4 per cent and abscess formation treated by reopening the lateral incision in 6 per cent. Twenty-one patients (10 per cent) have had recurrence and have needed reoperation.

Conclusion: Bascom's operation is simple and results in considerable financial savings with minimal social disruption and an early return to work. Recurrent disease is no more frequent than after other treatments.

Presented to the Association of Surgeons, Edinburgh, May 1998
Paper accepted 4 February 2000

British Journal of Surgery 2000, 87, 1067–1070

Introduction

Many procedures have been described for the management of symptomatic pilonidal sinus, none of which, judged by the yardsticks of primary healing and recurrence of disease, are perfect. Although simple shaving may control symptoms without operation[1], surgery is often required when chronic infection supervenes. Allen-Mersh, in a review article of 1990[2], described outcomes after treatment by a number of methods; the results are summarized in *Table 1*.

Ambulatory surgical treatments that are equally effective in treating disease but which offer rapid return to full activity are to be preferred over more complex surgical procedures[3,4]. The most difficult complication that may follow surgery for pilonidal disease is a persistently unhealed midline wound, most commonly seen after laying open or excision of the primary disease. The exact frequency of this is difficult to determine from the literature since many reports detail disease recurrence, rather than healing failure[5–7]. However, clinicians who manage this condition regularly are familiar with these painful wounds which prevent return to normal activity (particularly gainful employment), demand regular nursing and medical attention, and can persist for long periods of time.

Surgical procedures that keep the main wound away from the midline are most likely to succeed. Karydakis[8] described a technique of asymmetric closure with excellent results. Mann and Springall[9] have also described an asymmetric

Table 1 Summary of treatment for pilonidal sinus[2]

Method	Time to healing (days)	Recurrence/ failure (%)
Curettage of tract	21–52	3–24
Phenol injection	14–61	0–35
Wide excision and marsupialization	31–90	1–43
Primary closure	10–50	0–37
Asymmetric closure	8–16	0–5

excision and primary closure with good results, but with the use of general anaesthesia and a mean hospital stay of 16 days. This paper describes the results of pilonidal surgery by Bascom's technique[10,11], a day-case procedure undertaken with local anaesthesia which places the main wound away from the midline.

Patients and methods

Data were acquired prospectively from the surgical treatment of 218 patients (159 men) of mean age 27 (range 14–84) years with symptomatic pilonidal disease between 1992 and 1999. The mean duration of symptoms was 2·4 years. One hundred and ninety-one patients (88 per cent) had details of the disease recorded. Sixty-one patients (28 per cent) had only one or two midline pits. The remainder had more complex disease with several midline pits; 39 per cent had a lateral discharging sinus as evidence of a chronic abscess.

One hundred and eighty-three patients (84 per cent) had treatment performed under local anaesthetic and 73 opted for supplementary intravenous sedation. The remaining 35 patients (including children) were treated under general anaesthesia. Day-case treatment was planned for all patients.

Technique

Bascom's technique[10,11] was used. One hour before operation, patients were prescribed metronidazole 400 mg and cephadroxil 500 mg orally unless general anaesthesia was planned. This medication was repeated at 12 and 24 h after operation. Local anaesthesia was achieved by infiltration alone, with sedation offered to cover the immediate discomfort of anaesthetic administration if required. The preferred solution was a mixture of equal volumes of 1 per cent lignocaine, 0·5 per cent bupivacaine with 1 : 200 000 adrenaline, and normal saline. A total volume of 60 ml was adequate in all circumstances; often less than 30 ml was needed.

Midline pits were excised, removing a minimal amount of tissue (equivalent to a grain of rice) in each case (*Fig. 1*). Care was taken to identify all pits by stretching the postanal skin caudally; these wounds extended into the 'abscess' cavity which was then drained laterally to the most convenient side of the midline by means of a parallel incision at a distance of some 2–3 cm (*Fig. 2*). The abscess cavity was curetted, thereby removing all infected granulation tissue and hair. A fibrous and fatty flap (consisting of the wall of the abscess cavity opposite to the lateral drainage incision) was lifted, deep to the midline pits. This was achieved by incising the fibrous boundary of the abscess cavity into the fat of the opposite buttock, thus releasing the midline pits from the postsacral fascia. The thickness of this flap was the depth of the abscess cavity. This flap was sutured to the bridge of skin between the midline pits and the lateral drainage wound, and the midline wounds were closed with a subcuticular, non-absorbable suture (*Fig. 3*). Haemostasis was then secured using monopolar diathermy.

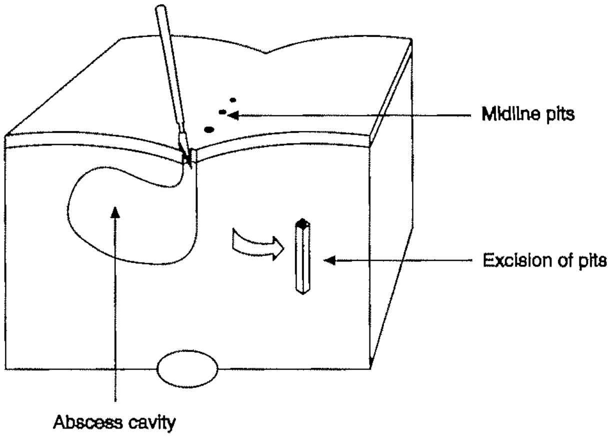

Fig. 1 Excision of midline pits

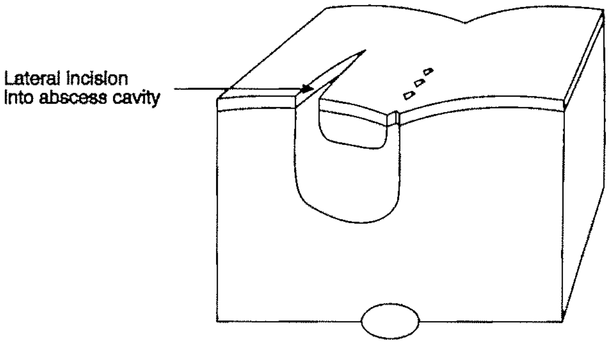

Fig. 2 Lateral drainage of abscess cavity

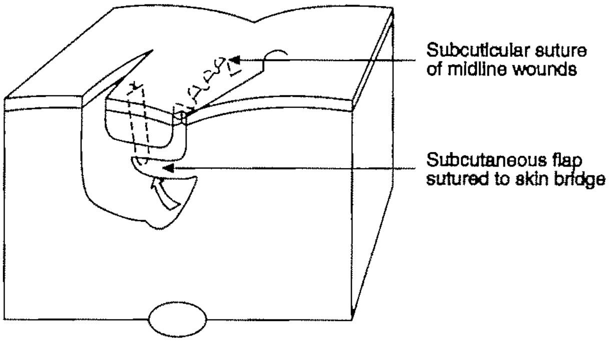
Subcuticular suture of midline wounds
Subcutaneous flap sutured to skin bridge

Fig. 3 Suturing of subcutaneous flap to skin bridge and subcuticular closure of midline wounds

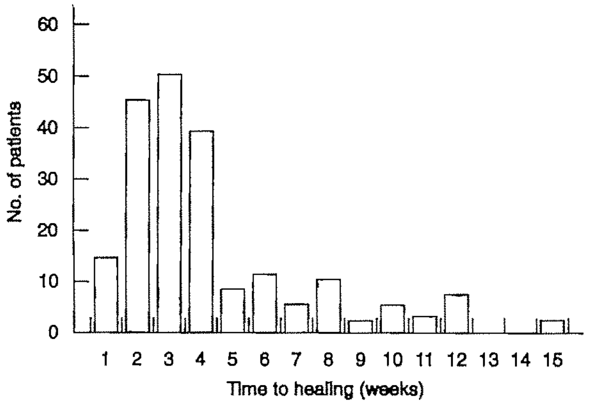

Fig. 4 Time taken to healing of lateral wounds

The lateral drainage wound was neither sutured nor packed and a light dressing was applied to absorb postoperative discharge. All sutures were removed after 1 week and patients were reviewed weekly until all wounds had healed. Patients were self-caring with no need for attention by a nurse.

Results

Patients usually returned to normal activities within a few days having needed minimal analgesia. Most returned to work within 2 weeks. No patient needed hospital admission for pain control. The mean duration of follow-up was 12·1 (range 1–60) months by either outpatient visits, phone calls or by postal questionnaire sent every 2 years. Only 11 patients (5 per cent) were lost to follow-up. All patients were asked to report any further symptoms from the pilonidal disease, even if managed elsewhere.

Wound healing

The midline wound failed to heal in only one patient, for whom it was necessary to undertake further surgery in the form of a Bascom 'cleft closure'[12]. In one patient the entire lateral wound epithelialized and required further surgery to excise the unwanted skin. All other lateral wounds healed at a mean of 4·0 (range 1–15) weeks (*Fig. 4*). These wounds sometimes had proud granulation tissue that was treated by application of silver nitrate.

Postoperative complications

Significant postoperative bleeding occurred in nine patients (4 per cent) which either stopped spontaneously with pressure or required diathermy. This complication may have been more frequent with intraoperative use of a dilute adrenaline solution.

Abscess formation occurred in 17 patients (8 per cent) as a result of too rapid closure of the lateral wound. In 1996 it was thought that suture of the subcutaneous flap to the skin bridge was not necessary and it was omitted in 29 consecutive patients. Abscess formation subsequently occurred in six of these 29 patients (21 per cent), significantly more frequently than when the bridge was sutured in 11 of 189 patients (6 per cent) ($\chi^2 = 5{\cdot}80$, 2 d.f., $P < 0{\cdot}01$). Once this situation was recognized, all bridges were sutured. Abscesses were treated by reopening the lateral incision.

Twenty-one patients (10 per cent) experienced further pilonidal symptoms requiring surgery. In 12 patients Bascom's operation was repeated with similar rates of healing. Two patients have had abscesses drained alone, five patients have had a Bascom's cleft closure and two patients have had further surgery elsewhere. Another 13 patients (6 per cent) have developed midline pits but have not yet required surgery.

Discussion

These results demonstrate that Bascom's procedure fulfils many of the requirements of the ideal operation for symptomatic pilonidal sinus. It is a simple procedure that is easy to teach and to undertake, and is suited to surgery under local anaesthetic and day-surgical conditions. In addition the patients are self-caring in the postoperative period. The results are comparable with the best of other series, with considerably less expenditure in terms of time spent in hospital and in nursing and medical attention. Although the results may not be as good as those of asymmetric closure techniques, Bascom's operation is considerably easier to perform.

The cost of a day-surgical pilonidal sinus operation is calculated as £483 compared with £853 for inpatient care. This has allowed a saving of £80 660 over the period of this report, not counting cost saving as a result of reduced nursing care in the postoperative period.

It is evident that minor difficulties remain with this procedure that may be ameliorated by attention to technical detail and perhaps by pharmacological advances, such as less painful local anaesthetic agents and safer sedation. Local anaesthetic infiltration is accompanied by considerable, although short-lived, pain until the anaesthetic takes effect. Although patients may be reassured that this is the only discomfort that will be experienced, it has resulted in the need for a substantial number of patients requesting sedation that may otherwise not be necessary.

Postoperative haemorrhage, although minor in the majority of instances, may result in the need for a general anaesthetic for control either by diathermy or packing. Appreciation of this possibility and the knowledge that dilute adrenaline solution has been employed should encourage the surgeon to be fastidious in the pursuit of haemostasis on completion of surgery. The problem of abscess formation in the healing wound, although troublesome, has been largely solved by suturing the wall of the chronic cavity to the skin bridge as already described. There remain, however, a few instances of this complication. The authors have noted that it is possible (with minimal patient discomfort) to digitate the lateral wound at the first postoperative visit, after sutures have been removed, to ensure drainage. This often releases a substantial collection of old blood that might otherwise have become infected.

It is not surprising that some patients experience recurrent disease. The aetiology of pilonidal sinus is poorly understood and it may be that the operation, as described, fails to remove the precipitating factors. Bascom's theory, that pits form under the influence of the gravitational pull on the postanal skin[12], may account for the success of the procedure in keeping recurrence to a minimum by detaching the midline skin from the postsacral fascia. However, after surgery, the potential exists for adhesions to form between the postanal skin and the postsacral fascia, which may account for some recurrent disease. In addition, the geometry of a deep natal cleft is not altered as in the case of asymmetric closure techniques. Pilonidal pits are known to occur in skin that has been moved to the midline from elsewhere[1]. Furthermore, missed pits may be a cause for persistent disease; surgeons must make every effort to identify and excise all disease existing at the time of surgery. It is apparent that patients outgrow the tendency to symptomatic pilonidal sinus disease, which is seldom seen over the age of 40 years[6]. Whether this is due to changes in the nature of the hair or postanal skin is unknown.

No treatment for pilonidal sinus disease is perfect, but even if the Bascom procedure fails it usually leaves a problem which is no worse than the original presentation. The same cannot be claimed for wide excision. The overall morbidity and wound care needed after Bascom's procedure is less than that after other surgical approaches. It may be, however, that for patients with a deep cleft or those who are particularly hairy, an asymmetric closure technique may be more appropriate.

The present results are in accord with a retrospective report of 41 patients operated on by the Bascom procedure in which further surgery for recurrent disease was needed in 7 per cent[17]. Length of follow-up in the present series was longer and the recurrence rate similar, testifying to the durability of the surgical outcome.

Treatments for pilonidal sinus should be compared in the context of rate of healing, morbidity and cost of outpatient care. Bascom's technique may be the procedure of choice in the initial surgical treatment of most symptomatic pilonidal sinus disease.

Acknowledgements

The authors are grateful to Dr John Bascom for help, encouragement and comments.

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Original article

Compression anastomosis (AKA-2) in colorectal surgery: results in 442 consecutive patients

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Background: The morbidity and mortality associated with colorectal surgery results partly from anastomotic leakage. Animal experiments have shown some advantages of sutureless anastomosis over conventional colorectal anastomosis. Compression anastomosis follows the same biological principles as sutureless anastomosis.

Methods: The compression anastomosis AKA-2 was evaluated in a prospective consecutive audit of 442 patients between September 1989 and August 1998.

Results: Anastomoses were performed in 372 elective and 70 emergency situations. The indication for operation was colorectal cancer (56·3 per cent) and diverticulitis (23·5 per cent). A defunctioning colostomy was performed in 110 patients (24·9 per cent). Fourteen patients died (3·2 per cent). Death was related to anastomotic complications in three patients (0·7 per cent). Twenty-four patients (5·4 per cent) developed intra-abdominal complications. There were 11 symptomatic (2·5 per cent) and six asymptomatic (1·4 per cent) leakages. Anastomoses that were more than 10 cm from the anal verge leaked in seven (2·4 per cent) of 291 cases, while anastomoses between 5 and 10 cm leaked in three (2·6 per cent) of 116 cases and those less than 5 cm from the anal verge leaked in one (3 per cent) of 35 cases.

Conclusion: The low incidence of anastomotic complications demonstrates good biological healing of compression anastomoses. The compression anastomosis AKA-2 is safe in both high and low anterior resection and can therefore be recommended for use in colorectal surgery.

Paper accepted 21 February 2000

British Journal of Surgery 2000, 87, 1071–1075

Introduction

The morbidity and mortality associated with colorectal surgery results partly from anastomotic leakage. The reported incidence of clinically apparent anastomotic leakage after low anterior resection is between 1 and 16 per cent[1–4]. The rate of asymptomatic leakage is known to be two to three times higher than the clinical leakage rate[5,6]. Up to half of postoperative deaths are reported to be caused by sepsis due to anastomotic leakage[1,7]. This has led to investigation of alternative anastomotic techniques to improve the safety of anastomosis. A promising alternative to hand-sewn and stapled anastomoses is the compression anastomosis.

Compression anastomotic devices have been available since the nineteenth century. In 1826 Denan conceived a sutureless bowel anastomosis which encompassed the inverting technique proposed by Lembert. In 1892 Murphy developed a 'button' that was used extensively, with considerable success[8–10]. In 1963 the technique of compression anastomosis was reinvestigated by Hallenbeck *et al.*[11] with the object of making low rectal anastomosis safer and easier to perform.

Animal experiments have shown that intestinal anastomoses can be performed without any foreign body. These sutureless anastomoses were found to be superior to conventional anastomoses using both functional and morphological criteria[12,13]. Compression anastomosis comes very close to the principle of sutureless anastomosis because the compression rings are only temporary.

Today there are two devices available for performing compression anastomosis. The AKA-2 device (Seidel Medipool, Munich, Germany) was developed by Kanschin *et al.*[14] in 1984 and the biofragmentable anastomosis ring (BAR), Valtrac (Davis and Geck/Cyanamid, Danbury, Connecticut, USA), was developed by Hardy *et al.*[8]. In contrast to the BAR, the AKA-2 rings are not resorbable and the device was made specifically for transanal application.

The results of using the AKA-2 anastomosis in 442 consecutive patients are presented.

Patients and methods

The sutureless compression anastomosis AKA-2 was performed in a consecutive prospective non-comparative clinical audit between September 1989 and August 1998 in 442 patients who required resection of the left colon and rectum. After 1995 patients with anastomoses lower than 6 cm and those having elective resection of the sigmoid colon for diverticulitis were excluded. These patients either underwent reconstruction with a colorectal or coloanal pouch–anastomosis or were treated by means of a laparoscopic technique.

The AKA-2 device performs an anastomosis with inverted bowel edges, which are pressed together by two intraluminal rings. On the basis ring (distal) metal pins with metal ring springs are attached (*Fig. 1*). The metal pins have barbs on the tips. When performing the anastomosis these tips first pass through the inverted bowel edges and then penetrate the proximal plastic ring (disc), where they are fixed by the barbs. Simultaneously circular blades cut the central cuff of bowel in a manner similar to conventional circular stapling. The metal springs ensure constant compression on the inverted bowel edges and the metal pins prevent the compressed intestinal walls from slipping out of the compression zone. The two plastic rings and the compressed resection margins separate from the anastomosis after 4–6 days and are excreted with the faeces. This results in a sutureless anastomosis.

The steps for preparing the bowel edges for anastomosis (preparation of the resection margins, placement of purse-string sutures) and the use of the AKA-2 device (*Fig. 2*) are similar to those required for an anastomosis performed with a circular stapling device. The plastic rings are available in 25, 28 or 31 mm diameter.

The device was used in both elective and emergency operations. All elective patients underwent orthograde bowel lavage the day before operation. Emergency patients underwent intraoperative bowel lavage. In all patients the rectal stump was irrigated during operation with polidone–iodine solution. Following anastomosis, the integrity of the anastomosis was checked by intraoperative testing with polidone–iodine solution, a Gastrografin (Schering, Berlin, Germany) enema between days 12 and 14 after operation, and lower gastrointestinal endoscopy between the second and fourth weeks.

Symptomatic and asymptomatic leakages were recorded as complications related to the abdominal procedure and to death.

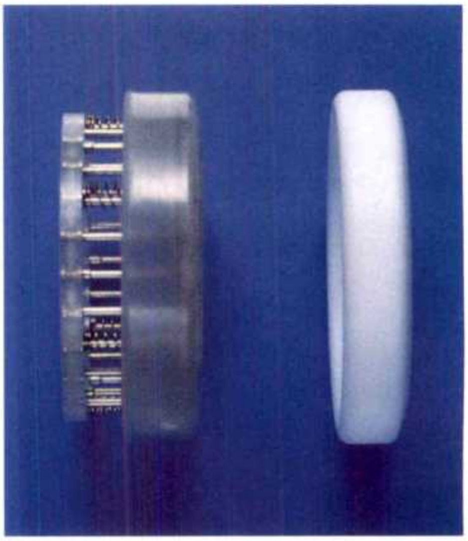

Fig. 1 AKA-2 compression anastomosis. Metal pins with metal ring springs are attached on the base ring (grey). When performing the anastomosis the pins penetrate through the inverted resection margins in the proximal plastic ring (white)

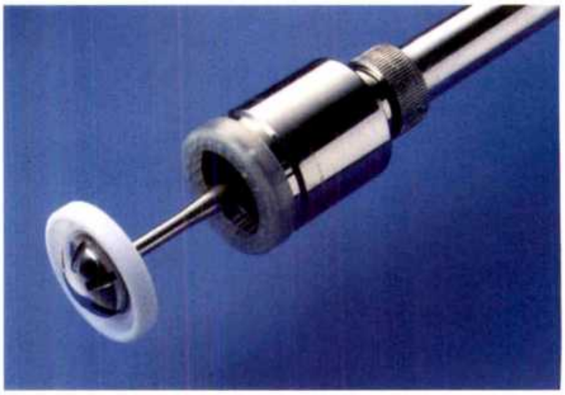

Fig. 2 The AKA-2 device. After insertion of the device through the anus, the rectal purse-string is tightened around the shaft above the distal ring (grey). The proximal bowel is then placed over the proximal ring (white) and the purse-string is also tightened around the shaft; anastomosis is performed in a similar manner as with the use of circular stapler devices

Results

Some 442 consecutive patients underwent colorectal resection with the AKA-2 anastomosis. The mean age was 70·6 (range 31–90) years. There were 228 men and 214 women (sex ratio 1 : 1). Indications for operation were colorectal cancer in 249 patients (56·3 per cent) and diverticulitis in 104 (23·5 per cent). Twenty patients had a resection because of Crohn's disease (*Table 1*). The remain-

Table 1 Indications for resection in 442 patients

Indication	No. of patients
Rectal cancer	73 (16·5)
Sigmoid cancer	151 (34·2)
Descending colonic cancer	25 (5·7)
Cancer recurrence	9 (2·0)
Diverticulitis	104 (23·5)
Crohn's disease	20 (4·5)
Gynaecological cancer	8 (1·8)
Other	52 (11·8)

Values in parentheses are percentages

Table 2 Indications for protective stoma

Indication	No. of patients
Multivisceral resection	31
High-risk patient	31
Colonic perforation	20
Ileus	18
Rectovaginal or rectovesical fistula	10
Total	110

Table 3 Postoperative complications in 442 patients

Complication	No. of patients
Anastomotic leakage	11 (2·5)
Asymptomatic leakage	6 (1·4)
Abscess	2 (0·5)
Bleeding	3 (0·7)
Stenosis	2 (0·5)
Total	24 (5·4)

Values in parentheses are percentages

Table 4 Clinically apparent leakage according to the level of anastomosis

Level of anastomosis	All patients	Patients without colostomy
< 5 cm	1 of 35 (3)	1 of 22 (5)
5–10 cm	3 of 116 (2·6)	2 of 72 (3)
< 10 cm	4 of 151 (2·6)	3 of 94 (3)
> 10 cm	7 of 291 (2·4)	6 of 187 (3·2)
Total	11 of 442 (2·5)	9 of 332 (2·7)

Values in parentheses are percentages

ing patients had rectovaginal or rectovesical fistula or large colorectal adenoma. The majority of colorectal cancers were located in the sigmoid colon ($n = 151$), followed by the rectum ($n = 73$). One hundred and twenty-nine patients were found to have pathological tumour (pT) stage 3 tumours, 75 patients had pT_4 tumours, 32 had pT_2 and 13 had pT_1 tumours. Positive nodes were found in 154 patients (61·9 per cent). Fifty-three patients (21·3 per cent) had distant metastases. During curative resection of the colon and rectum, high ligation of the inferior mesenteric vessels was regularly performed.

In all, 70 patients underwent emergency resection. Bowel perforation was found in 44 patients (33 had diverticulitis, 11 had cancer) and obstruction in 26 (21 patients with cancer, five with diverticulitis).

The operations performed included high anterior resection ($n = 177$; 40·0 per cent), low anterior resection ($n = 108$; 24·4 per cent), sigmoid resection ($n = 98$; 22·2 per cent), left hemicolectomy ($n = 27$; 6·1 per cent), subtotal colectomy ($n = 21$; 4·8 per cent) and 11 anastomoses after Hartmann's procedure (2·5 per cent). Low anterior resection (defined by the anastomosis below the peritoneal reflection) was performed in patients with rectal cancer, some with gynaecological cancer and low sigmoid cancer, rectovaginal and rectovesical fistula, large adenomas of the rectum and some patients with diverticulitis.

The colorectal anastomosis was more than 10 cm from the anal verge in 291 patients (65·8 per cent), between 5 and 10 cm in 116 (26·2 per cent) and less than 5 cm in 35 patients (7·9 per cent).

A protective colostomy was performed in 110 patients (24·9 per cent). The rate of protective colostomy was higher in the emergency group (38 (54·3 per cent) of 70 patients) than in the elective group (72 (19·4 per cent) of 372). The reasons for colostomy are shown in *Table 2*.

Complications

Fourteen patients (3·2 per cent) died during the postoperative period. Causes of death were mostly pulmonary ($n = 5$) and extra-abdominal septic ($n = 4$) complications. One patient died after myocardial infarction, another from splenic abscess due to sepsis. Death was related to anastomotic leakage in three patients (0·7 per cent).

Complications relating to the abdominal procedure occurred in 24 patients (5·4 per cent) (*Table 3*). Two patients had intra-abdominal abscesses. Three patients required reoperation because of bleeding, and anastomotic stenosis occurred in two patients (0·5 per cent). These were treated by bouginage. Symptomatic anastomotic leakage occurred in 11 patients (2·5 per cent). Asymptomatic leakage was found in a further six patients (1·4 per cent).

Anastomotic leakage

Clinically apparent anastomotic leakage occurred in 11 patients (2·5 per cent) including three patients who died (*Table 4*). Ten leaks were found after elective resection (ten (2·7 per cent) of 372 patients – five with rectal cancer, two with sigmoid cancer, one with Crohn's disease, one with rectal prolapse, one with diverticulitis). Two of these patients were receiving corticosteroids. One leak appeared after emergency resection for complicated diverticulitis (one (1 per cent) of 70 patients).

Anastomoses more than 10 cm from the anal verge leaked in seven (2·4 per cent) of 291 patients, whereas anastomoses lower than 10 cm leaked in four (2·6 per cent) of 151 patients. Anastomoses below 5 cm showed a slightly higher leakage rate (one (3 per cent) of 35 patients). The incidence of leakage was not significantly different in patients with and without a defunctioning colostomy (two of 110 *versus* nine of 332). Treatment of leakage included Hartmann procedure in four patients, construction of a new anastomosis and defunctioning colostomy in four patients and a defunctioning colostomy in three. Gastrografin enema revealed a further six asymptomatic leakages (1·4 per cent) that required no treatment. Sigmoidoscopy between the second and fourth week after operation showed complete epithelialization of the anastomosis.

Discussion

Animal experiments have shown the advantages of sutureless anastomosis over hand-sutured and conventional stapled anastomoses, even under conditions of experimental peritonitis[12,13]. Similar results were found with compression anastomoses[8,10,11,15].

When the authors started to perform compression anastomosis two devices were available: the AKA-2 and the BAR, Valtrac. The AKA-2 was chosen because at that time it was the only compression anastomosis device made for transanal application, and the authors wished to evaluate compression anastomosis in situations where circular stapler devices were usually used.

The main difference between the AKA-2 and the Valtrac is the manner in which the rings are expelled. While necrosis of the inverted resection margins is the only (biological) factor leading to rejection of the plastic rings in AKA-2 anastomosis, it is mainly fragmentation of the plastic rings in Valtrac anastomosis. The later rejection of the Valtrac ring (day 16–23) in contrast to the AKA-2 ring (day 4–6) may be an advantage in conditions of delayed anastomotic healing. There are two potential disadvantages of the Valtrac. One is that during the closure of the Valtrac rings the bowel near the anastomosis may be contused by the closing manoeuvre from outside the gut. The other is the potential risk of relative obstruction due to the smaller inner diameter of the Valtrac in comparison with the AKA-2. There are, however, no trials dealing with these differences.

The present series summarizes the authors' experience of a large number of consecutive resections with compression anastomosis (AKA-2) on the left-sided colon and rectum. The study was performed to evaluate the safety and potential advantages of compression anastomosis in humans. As indicators of healing, symptomatic leakage, asymptomatic leakage, the endoscopic appearance and complications related to the abdominal procedure were recorded. The rate of clinically apparent leakage was approximately 2·5 per cent in all patients and 2·6 per cent in patients with anastomosis less than 10 cm from the anal verge, and is low compared with that in other series. The range of reported rates of clinically apparent leakage varies from 1 to 16 per cent, with a majority indicating 3–8 per cent[2,3,6,7,16–18].

When the anastomosis was performed more than 5 cm from the anal verge, no difference in the anastomotic leak rate was observed. Anastomoses lower than 5 cm showed a slightly higher rate of leakage (3 per cent) especially when performed without colostomy (one (5 per cent) of 22 patients). This finding may relate to the small number of patients in this group. However, low anastomoses are known to have a higher rate of leakage than intraperitoneal anastomoses[1–3,19].

In the present patients, a defunctioning colostomy did not have an influence on the rate of symptomatic leakage (1·8 *versus* 2·7 per cent). Furthermore, an influence of defunctioning colostomy on anastomotic wound healing has not yet been proven. Senagore *et al.*[20] showed that proximal colostomy does not affect colonic wound healing in an animal model; however, as most anastomotic leakages in anastomoses protected by colostomy or ileostomy are asymptomatic, these have to be included to determine the true leak rate. Therefore, all the present patients had a Gastrografin enema performed between the 12 and 14 days after operation to evaluate the incidence of asymptomatic anastomotic leakage. The rate of asymptomatic leakage (1·4 per cent) in this study is very low in comparison with that of other series, which show a rate of asymptomatic leakage that is two to three times higher than that of clinically apparent leakage, with a reported incidence of 24 per cent[1,5,6]. This may be important because an increased risk of tumour recurrence according to clinical or subclinical anastomotic fistulas has been suggested[21]. There is also evidence that leakage with pelvic sepsis results in functional impairment after low anterior resection and total rectal resection[22]. Furthermore an effect of anastomotic technique on local tumour recurrence has been suggested several times but has not been proven[23–25].

The overall mortality rate in this series was 3·2 per cent, which compares with a reported mortality rate after resection of the distal colon and rectum of 1–6 per cent, with a median of approximately 3·5 per cent[3,5,16,17,19]. Three (0·7 per cent) of the present patients died as a consequence of anastomotic complications. Only a few other authors have reported their death rate in relation to failure of the anastomosis, with rates from 0·8 to 1·6 per cent[2,3,5,7].

The low incidence of clinical and asymptomatic leakage with the use of the sutureless compression anastomosis AKA-2 demonstrates the biological healing of compression anastomoses in humans. These results support the advantages of sutureless and compression anastomoses that were demonstrated in animal studies and show that the compression anastomosis AKA-2 is safe in high and low anterior resection with a low incidence of anastomotic complications. The results suggest that there may be clinical advantages of compression anastomosis over conventional stapled anastomosis.

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Original article

Analysis of risk factors for nosocomial sepsis in surgical patients

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Background: This study aimed to identify patients at high risk for developing sepsis following surgery according to criteria determined by the American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference on sepsis.

Methods: A prospective case–control study was performed in surgical patients in a tertiary care centre over 1 year. Patients were identified by a daily prospective surveillance. Controls were selected randomly from the daily list of surgical inpatients. Data were collected prospectively. Crude and adjusted odds ratios (ORs) and their 95 per cent confidence intervals were computed using logistic regression analysis.

Results: During follow-up, 99 cases and 99 controls were identified. The main risk factors for sepsis found in the multivariate analysis were coma within 48 h before sepsis (OR 13·5, 95 per cent confidence interval 3·6–50·8), low serum albumin level at admission (OR 15·8, 5·4–46·4), two or more intrinsic co-morbidities (OR 11·8, 2·8–49·4) and parenteral nutrition (OR 5·1, 1·5–17·1). Emergency surgery (OR 3·0, 1·4–6·4), abdominal surgery (OR 2·6, 1·0–6·8) and number of surgical interventions (OR 2·5, 1·1–6·1) were the variables related to surgery that significantly increased the risk of sepsis. Both the study on the Efficacy of Nosocomial Infection Control (SENIC) and the National Nosocomial Infections Surveillance indices showed a statistically significant trend with sepsis.

Conclusion: Patient-related factors appear to represent the greatest risk for developing postoperative nosocomial sepsis, rather than factors associated with the surgery.

Paper accepted 28 January 2000

British Journal of Surgery 2000, 87, 1076–1081

Introduction

During recent years significant advances have been made in the diagnosis and management of surgical infections and most efforts have been focused on prevention of surgical site infection (SSI)[1–3]. Risk factors for the development of SSI have been studied mainly in general surgical patients[4,5], although several studies have suggested that the risk of acquiring a nosocomial infection varies by type of procedure[1,6]. Even though SSI is the most common type of infection following surgery[1], the development of nosocomial sepsis and septic shock after surgery is one of the major causes of death[1,7]. Nevertheless, until recently there was no standardized terminology for sepsis which permitted comparison of different studies. In 1991 the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM) proposed new definitions for sepsis that are widely accepted in the USA as well as in Europe[8,9].

To date, no study on the risk factors for development of sepsis in all surgical patients has been published. The first epidemiological studies of sepsis that provide a prospective validation of the ACCP/SCCM criteria for sepsis have been reported[10,11], but these were conducted in the intensive care setting rather than in surgical wards. The main objective of this study was to identify patients at high risk for developing sepsis after operation using the new criteria for sepsis.

Patients and methods

A case–control study was performed in a 1200-bed tertiary care centre with a referral population of 525 000, between 1

Table 1 Characteristics of the study population

	Cases ($n=99$)	Controls ($n=99$)	P
Sex			0·14†
Male	72 (73)	60 (61)	
Female	27 (27)	39 (39)	
Severity of illness*			0·16†
Non-fatal	32 (32)	46 (46)	
Ultimately fatal	57 (58)	48 (48)	
Rapidly fatal	10 (10)	5 (5)	
Previous nosocomial infection	20 (20)	8 (8)	<0·05†
No. of surgical interventions			
1	70 (71)	88 (89)	
2	26 (26)	9 (9)	
3	3 (3)	2 (2)	
Mean(s.d.) age (years)	59·2(19·5)	61·6(16·6)	0·70‡
Mean(s.d.) no. of diagnoses	10·0(5·6)	4·9(3·8)	<0·001‡

Values in parentheses are percentages unless otherwise indicated. *McCabe–Jackson criteria. †Two-tailed χ^2 test; ‡two-tailed Student *t* test

Table 2 Type of operative procedures in cases and controls

	Cases ($n=131$)	Controls ($n=112$)	P†
Nervous system	12 (9·2)	2 (1·8)	0·03
Head and neck	10 (7·6)	13 (11·6)	
Thoracic and respiratory system	4 (3·1)	3 (2·7)	
Cardiovascular system			
Cardiac and coronary surgery	12 (9·2)	9 (8·0)	
Vascular surgery	15 (11·5)	11 (9·8)	
Haemic and lymphatic system (including splenectomy)	6 (4·6)	3 (2·7)	
Oesophagus/stomach	14 (10·7)	2 (1·8)	0·01
Small bowel/colon	11 (8·4)	3 (2·7)	
Appendicectomy	0 (0)	3 (2·7)	
Anus/rectum	6 (4·6)	2 (1·8)	
Liver/biliary tract (including cholecystectomy)	8 (6·1)	2 (1·8)	
Other digestive system	9 (6·9)	1 (0·9)	
Genitourinary system	4 (3·1)	7 (6·3)	
Open reduction of fracture	6 (4·6)	3 (2·7)	
Joint prosthesis	1 (0·8)	10 (8·9)	0·004
Limb amputation	3 (2·3)	6 (5·4)	
Other musculoskeletal system	7 (5·3)	23 (20·5)	<0·001
Skin	3 (2·3)	9 (8·0)	

Values in parentheses are percentages. †Two-tailed χ^2 test

December 1994 and 30 November 1995. The mean admission rate was 30 000 patients per year.

A case was defined as a surgical patient who developed a nosocomial sepsis during the study period according to the criteria of the ACCP/SCCM Consensus Conference on sepsis[8]. Nosocomial infections other than sepsis were diagnosed using the Centers for Disease Control and Prevention criteria[12,13]. The exclusion criteria were age less than 15 years, severe granulocytopenia (a polymorphonuclear leucocyte count of less than 500 cells/μl), human immunodeficiency virus infection, patients with organ transplants and patients transferred to/from other hospitals. Cases were identified using a daily prospective surveillance based on review of all the clinical records of surgical patients plus a daily surveillance report from the microbiology laboratory of all positive blood cultures. Controls were selected randomly from the daily list of surgical inpatients admitted at the same time as the cases. The exclusion criteria were the same as for cases.

All patients were monitored prospectively until discharge from hospital. Data were gathered on the following variables. Intrinsic factors (existing at admission) included sex, age, cancer, diabetes, renal failure, serum albumin level, presence or absence of mental status change according to the Glasgow coma score[10], severity of illness (classified according to the criteria proposed by McCabe and Jackson[14]), etc. Extrinsic risk factors related to health care included use of intravenous and urinary catheters, mechanical ventilation, parenteral nutrition, etc. Information on variables associated with surgery was also collected, including type of intervention, type of surgical wound, duration of surgery, antibiotic prophylaxis and the American Society of Anesthesiologists (ASA) preoperative assessment score. The SENIC index[15] and the National Nosocomial Infections Surveillance (NNIS) index[16] were computed.

Statistical analysis

Odds ratios (ORs) and their 95 per cent confidence intervals were calculated. ORs were adjusted for several variables by logistic regression; the variables included in the model of regression were those that met the criteria for confounders. In the final model those variables that changed the coefficient of the dependent variable by more than 10 per cent were retained[17,18]. Explicit statistical tests for trend across exposure levels in continuous variables were performed following the recommendations made by Thompson[19]. Statistical analyses were performed using Epi Info 6.0 (Centers for Disease Control, Atlanta, Georgia, USA)[20] and the BMDP statistical package (Dynamic version) (BMDP Statistical Software, Los Angeles, California, USA)[21].

Results

During the study period 99 cases and 99 controls were studied. Sepsis with bacteraemia occurred in 43 per cent of cases and 57 per cent of patients had a sepsis with culture-documented infection other than in the blood. The most

Table 3 Risk factors existing at admission and related to health care

Risk factor	Cases (*n*=99)	Controls (*n*=99)	Crude odds ratio	Adjusted odds ratio
On admission				
Severity of illness*†				
Non-fatal	32	46	1	1
Ultimately fatal	57	48	1·7 (0·9–3·2)	3·0 (1·2–7·2)
Rapidly fatal	10	5	2·9 (0·8–10·8)	3·3 (0·6–17·7)
Coma‡	34	3	16·7 (4·7–71·5)	13·5 (3·6–50·8)
Serum albumin (mg/ml)‡				
≥ 39	13	52	1	1
36–39	14	9	5·2 (1·5–19·0)	5·3 (1·7–16·1)
≤ 35	37	10	17·4 (6·0–52·9)	15·8 (5·4–46·4)
*P***			< 0·001	< 0·001
Complications before sepsis‡	66	36	3·5 (1·9–6·6)	2·9 (1·5–5·8)
No. of intrinsic co-morbidities‡				
0	17	42	1	1
1	39	37	2·6 (1·2–5·7)	2·9 (1·3–6·7)
2	27	16	4·2 (1·7–10·6)	4·5 (1·6–12·5)
> 2	16	4	9·9 (2·6–41·4)	11·8 (2·8–49·4)
*P***			< 0·001	< 0·001
Related to health care				
ICU stay§	49	16	5·1 (2·5–10·5)	3·0 (1·4–6·6)
Parenteral nutrition¶	40	4	16·1 (5·2–56·0)	5·1 (1·5–17·1)
Nasogastric tube¶	76	28	8·4 (4·2–16·8)	4·5 (1·9–10·3)
No. of extrinsic risk factors§				
1–3	13	48	1	1
4–6	28	36	2·9 (1·2–6·8)	1·1 (0·4–3·1)
> 6	58	15	14·3 (5·8–36·3)	4·3 (1·4–13·1)
*P***			< 0·001	< 0·001

Values in parentheses are 95 per cent confidence intervals. Serum albumin values not available in 35 cases and 28 controls. *McCabe–Jackson criteria. †Adjusted odds ratio (OR) for age, sex, neoplasm, diabetes, hepatopathy, coma and renal failure; ‡adjusted OR for age, sex, severity of illness and number of intrinsic co-morbidities; §adjusted OR for age, sex, number of intrinsic co-morbidities, duration of operation, SENIC index and number of surgical interventions; ¶adjusted OR for age, sex, number of intrinsic co-morbidities, duration of operation, SENIC index, number of surgical interventions, nasogastric tube and indwelling urinary catheter. ICU, intensive care unit. **Two-sided *P* values for linear trend test by logistic regression analysis. SENIC, Study on the Efficacy of Nosocomial Infection Control

common sources of infection were the surgical site (32 per cent), lower respiratory tract (27 per cent), intravenous catheter (15 per cent) and urinary tract (12 per cent). A primary source of sepsis occurred in 10 per cent of cases. The probability of acquiring a secondary nosocomial sepsis varied with the type of SSI: organ/space SSI in 19 per cent and deep SSI in 13 per cent. There was no case of sepsis with a superficial SSI as source.

There were no significant differences between cases and controls regarding age and sex (*Table 1*). Cases suffered more underlying conditions and with a greater severity than controls. There was a significantly higher proportion of nervous system and gastro-oesophageal procedures in cases than in controls (*Table 2*). Joint prosthesis and musculoskeletal system procedures were significantly more frequent in controls than in cases.

After adjusting for confounders, the main risk factors existing at admission were (*Table 3*) presence of coma within 48 h before sepsis (OR 13·5, 95 per cent confidence interval 3·6–50·8) and serum albumin level 35 dg/dl or less at admission (OR 15·8, 5·4–46·4). Other variables significantly related to sepsis were the severity of illness and the development of any complication before sepsis. There was a dose–response relationship with the number of intrinsic co-morbidities ($P < 0·001$).

Regarding health care-related variables (*Table 3*), just three factors were found to be significant in the adjusted analysis: intensive care unit (ICU) stay (OR 3·0, 1·4–6·6), parenteral nutrition (OR 5·1, 1·5–17·1) and nasogastric tube (OR 4·5, 1·9–10·3). A significant association was also found with the number of extrinsic risk factors showing a significant trend.

The risk of infection according to surgery-related variables is detailed in *Table 4*. Emergency surgery (adjusted OR 3·0, 1·4–6·4), abdominal operation (adjusted OR 2·6, 1·0–6·8) and number of surgical interventions (adjusted OR 2·5, 1·1–6·1) were factors that significantly increased the risk of sepsis. Both the SENIC index and the NNIS index

Table 4 Risk factors related to surgery

Risk factor	Cases (*n*=99)	Controls (*n*=99)	Crude odds ratio	Adjusted odds ratio
Emergency surgery*	41	19	3·0 (1·5–5·6)	3·0 (1·4–6·4)
Abdominal operation*	43	13	5·1 (2·4–11·0)	2·6 (1·0–6·8)
Antibiotic prophylaxis*	78	75	1·2 (0·6–2·4)	0·5 (0·2–1·3)
Surgical interventions ≥ 2*	29	11	3·3 (1·5–7·6)	2·5 (1·1–6·1)
Duration of operation (min)*				
≤ 60	10	22	1	1
61–120	29	30	2·1 (0·8–5·8)	2·4 (0·8–7·1)
121–240	38	34	2·5 (0·9–6·5)	0·8 (0·3–2·4)
≥ 241	22	13	3·7 (1·2–11·8)	0·6 (0·2–2·2)
P‡			< 0·05	0·24
Type of surgical wound*				
Clean	42	61	1	1
Clean–contaminated	32	18	2·5 (1·2–5·4)	1·0 (0·4–2·4)
Contaminated	13	9	2·1 (0·7–5·8)	0·4 (0·1–1·2)
Dirty	12	11	1·6 (0·6–4·2)	
ASA score*				
I	6	15	1	1
II	15	34	1·1 (0·3–4·0)	0·5 (0·1–2·0)
III	32	22	3·6 (1·1–12·6)	1·2 (0·3–5·9)
IV–V	17	7	6·1 (1·4–27·9)	1·2 (0·2–7·1)
P‡			< 0·001	< 0·18
SENIC index*				
0–1	20	48	1	1
2	48	43	2·7 (1·3–5·5)	2·3 (1·1–4·7)
3	21	6	8·4 (2·7–27·6)	7·1 (2·3–21·9)
4	10	2	12·0 (2·2–87·8)	15·5 (2·8–85·1)
P‡			< 0·001	< 0·001
NNIS index†				
0	11	38	1	1
1	55	41	4·6 (2·0–11·0)	3·8 (1·6–9·1)
2	27	18	5·2 (1·9–14·2)	3·5 (1·3–9·2)
3	6	2	10·4 (1·5–88·1)	11·0 (1·7–73·1)
P‡			< 0·001	< 0·01

Values in parentheses are 95 per cent confidence intervals. American Society of Anesthesiologists (ASA) score not available in 29 cases and 21 controls. *Adjusted odds ratio (OR) for age, sex, number of intrinsic co-morbidities, SENIC index, number of surgical interventions and previous nosocomial infection. †Adjusted OR for age, sex, number of intrinsic co-morbidities, number of surgical interventions and previous nosocomial infection. ‡Two-sided *P* value for linear trend test by logistic regression analysis. NNIS, National Nosocomial Infections Surveillance; SENIC, Study on the Efficacy of Nosocomial Infection Control

showed a clear and statistically significant trend with nosocomial sepsis, although the OR was greater for the SENIC index than for the NNIS index.

Table 5 summarizes the main risk factors for nosocomial sepsis. The most significant factors were presence of coma within 48 h before sepsis, low serum albumin level at admission, two or more intrinsic co-morbidities, administration of parenteral nutrition and a SENIC or NNIS index score greater than 2.

Discussion

Data reported from the NNIS showed that nearly 5 per cent of nosocomial infections in surgery had an associated secondary bloodstream infection[1]. This figure may be greater if the new definitions of sepsis are taken into account rather than just sepsis with bacteraemia. However, the risk factors influencing the development of sepsis in surgical patients remain unclear. The probability of acquiring a secondary bacteraemia varied significantly with the site of infection; organ/space SSI and pneumonia were the most frequent sources[1], and these facts are in accordance with the present results for overall sepsis. On the other hand, it has been suggested that the risk of acquiring a nosocomial infection also varies by type of procedure[1,6]. The results presented show a higher proportion of nervous system and gastro-oesophageal procedures and a lower proportion of joint prosthesis and musculoskeletal system procedures in cases than in controls.

Table 5 Summary of risk factors for the development of nosocomial sepsis in surgical patients

Variable	Increased risk
Risk factors existing at admission	
Severity of illness*	+
Coma	++
Serum albumin (< 40 dg/dl)	++
Development of complications before sepsis	+
No. of intrinsic co-morbidities (> 2)	++
Risk factors related to health care	
ICU stay	+
Parenteral nutrition	++
Nasogastric tube	+
No. of extrinsic risk factors (> 6)	+
Risk factors related to surgery	
Emergency surgery	+
Abdominal operation	+
SENIC index	++
NNIS index	++
ASA score	+/–
Contaminated–dirty surgical wound	+/–
Duration of intervention	+/–
Antibiotic prophylaxis	+/–

+/–, Odds ratio (OR) less than 1·5 or not significant in the adjusted analysis; +, OR between 1·6 and 4·9 in the adjusted analysis; ++, OR 5 or more in the adjusted analysis. *According to McCabe–Jackson criteria. ICU, intensive care unit; SENIC, Study on the Efficacy of Nosocomial Infection Control; NNIS, National Nosocomial Infections Surveillance; ASA, American Society of Anesthesiologists

The risk factors for SSI are relatively well established and have been considered in several epidemiological studies[3,4,22]. The risk factors identified were mainly related to the type of operation, skill of the surgical team and patient characteristics[4]. In the present study the main risk factors for nosocomial sepsis in surgical patients were variables related to their underlying conditions, including the presence of coma in the 48 h before sepsis, a low serum albumin level at admission and the number of intrinsic risk factors identified. It has been reported that coma is associated with a high risk of nosocomial pneumonia, especially in patients undergoing upper abdominal surgery[23]. Nosocomial pneumonia is frequently associated with sepsis and in this study the respiratory tract was the second commonest source of sepsis. Serum albumin is an indicator of malnutrition, and the relationship between malnutrition and infection is established[24].

It has been shown that ICU stay increases the risk of nosocomial infection[10,11]. The present results agree with this. Other health care factors that indirectly indicate the severity of any underlying condition, such as use of a nasogastric tube and parenteral nutrition, also increased the risk of sepsis.

Surgery-related risk factors for SSI were not identified for sepsis, including wound contamination, duration of operation or chemoprophylaxis[3], despite the fact that SSI was the more frequent source of sepsis. Nevertheless, the types of SSI involved were organ/space and deep SSI, the most severe types; there was no sepsis resulting from an incisional SSI. The same has been found in a large study of risk factors for neurosurgical site infection after craniotomy[25]. These facts suggest that the underlying conditions of the patients influence the risk of organ/space and deep SSI more than incisional SSI.

There are two measures of intrinsic patient risk in surgical patients, the SENIC index[15] and the NNIS index[16]. Both are good predictors of SSI[26] and postoperative pneumonia[27]. The present results show that the risk of sepsis significantly increased with both indices, although the OR was greater for the SENIC index. This may be because the SENIC index takes into account two independent risk factors for sepsis, abdominal surgery and number of diagnoses at discharge (as an estimate of the number of intrinsic co-morbidities), whereas the NNIS index uses the wound class and duration of operation, which were unrelated to sepsis in this study.

Several criticisms of the present study might be raised. First, it is unlikely that the exclusion criteria have introduced a selection bias because the excluded patients are well defined groups with an increased risk of nosocomial bloodstream infection[28,29]. However, the exclusion criteria could limit the overall generalizability of the results to all surgical patients with sepsis. Another factor that may limit the validity of the conclusions of this study could be sample size; a small sample size may lack the statistical power to detect some associations. This may have obscured the identification of some risk factors for sepsis, mainly those with small influence.

In summary, the present results suggest that patient-related factors represent the greatest risk for postoperative nosocomial sepsis, rather than factors related to the surgery. Identification of patients at high risk of developing postoperative nosocomial sepsis, and prevention and/or treatment of predisposing conditions such as coma or malnutrition, may contribute to improving their prognosis.

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Original article

Impact of the '2 week wait' directive for suspected cancer on service provision in a symptomatic breast clinic

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Background: The '2 week wait' directive (Health Service Circular (HSC) 1998/242) guaranteeing that 'everyone with suspected breast cancer will be able to see a specialist within two weeks of their general practitioner (GP) deciding they need to be seen urgently' is a unique audited approach to access for the British National Health Service, the effects of which have been assessed in a non-academic symptomatic breast clinic.

Methods: New GP referrals ($n = 607$) were reviewed prospectively in two comparable 3-month intervals, beginning 1 April 1998 and 1 April 1999, to determine the probability of a breast cancer diagnosis from the referral letter and the effects of the directive on waiting times for appointments and utilization of clinics.

Results: The urgency of referral was not specified in 53 per cent of GP referrals. For the 'urgent' cases (25 per cent of all new referrals) the probability of a final diagnosis of breast cancer was 0·19. The breast specialists prospectively achieved a rate of 0·26 from 99 per cent of the same referral letters. 'Urgent' referrals did not wait significantly longer in 1999 (median 9 *versus* 10 days) but waiting times for new appointments overall increased (13 *versus* 16 days; $P < 0{\cdot}01$), and this was greatest for 'routine' referrals (14 *versus* 21 days; $P < 0{\cdot}001$). These changes were caused by an increase in the number of clinic appointments, due to significant increases in median number of visits to diagnosis or discharge and clinic non-attendance in 1999, resulting in overbooking. Telephonic communications were associated with faster median access times (fax 8 days; telephone 2 days), relative to mailed referrals (19 days) ($P < 0{\cdot}01$).

Conclusion: Breast specialists were better overall at assessing the probability of a breast cancer diagnosis. The waiting time for 'urgent' appointments was unchanged following HSC 1998/242, but there was an increased wait for other patients, especially those assessed as having a lower probability of cancer.

Paper accepted 20 April 2000

British Journal of Surgery 2000, 87, 1082–1086

Introduction

The '2 week wait' directive (Health Service Circular (HSC) 1998/242), which *guarantees* that 'everyone with suspected breast cancer will be able to see a specialist within two weeks of their general practitioner (GP) deciding they need to be seen urgently', was implemented on 1 April 1999[1]. The authors are not aware of any comparable initiative in Europe or Australasia, although guidelines for referral are commonplace (R. Robertson, New Zealand, B. Ritchie, Canada, R. Vogel, Germany, K. Hosie, Plymouth, I. Struyt, Brussels, M. Fitzgerald, European Commission, H.H. Hanson, EMSO, F. Pilkiewicz, EMSO, personal communication). Rapid access is to be applauded, although there is no evidence that the 14-day target effects the outcome in breast cancer and debate continues over the effect of delays as long as 6 months[2]. Psychological factors are a different issue; delay may influence anxiety levels for benign as well as malignant disease and the association with outcome is uncertain[3].

Traditionally, hospital specialists have determined the urgency of outpatient appointment. The likelihood of breast cancer can be predicted from the presenting symptomatology[4] and, furthermore, GP guidelines have the potential to decrease unnecessary referrals without increasing the delay in diagnosing cancer[5]. Thus, risk assessment by the GP is feasible, supported by the specified National Health Service (NHS) guidelines[6].

In this study a prospective breast clinic database was used to audit the probability of a diagnosis of cancer from the GP referral letter. The effect of the directive on waiting times for urgent and non-urgent breast referrals was reviewed and the factors that determined the wait for an appointment were assessed.

Patients and methods

A prospective breast clinic database was searched for patient details in two time intervals: 1 April to 30 June 1999, which followed the imposition of the 2-week wait directive, and 1 April to 30 June 1998, a similar period a year previously. Only new patients referred by the GP were included; all others such as screen-detected, old, re-referral and hospital patients were excluded. The changes consequent upon HSC 1998/242 involved preferential allocation of the next available clinic appointment to the cases specified as 'urgent'. A dedicated fax line was installed to the breast office where referrals were processed by a single dedicated team, as opposed to two surgical offices previously. National[5] and local referral guidelines were sent to all registered GPs and a regional meeting was convened to inform them of these changes. No funding accompanied the directive during the study interval.

For each GP referral letter the risk stratification ('urgent', 'soon' or 'routine'), if specified, was recorded, as was the category allocated to the patients by either of the two specialist breast surgeons concerned. To an extent both assessments were arbitrary but a broad categorization was as follows. A significant objective symptom (lump, ulcer, tethering or swelling) in a patient over 40 years was classified as 'urgent'. The risk stratification was 'soon' for an objective symptom (lump, etc.) in a patient under 40 years or others (nipple discharge, nodularity, thickening) at any age. Subjective symptoms such as pain or family history concerns were categorized as 'routine'. The risk stratifications were compared with the final diagnosis of 'cancer' and 'not cancer'.

Dates recorded and analysed were date of referral by GP by letter/fax/telephone (*a*); date of receipt of referral by specialist in breast office (*b*); date of appointment offered to patient (*c*); and date of consultation (*d*).

The waiting times (in days) were defined as: total delay (*a* minus *d*); referral delay (*a* minus *b*), the delay in the referral process from GP to specialist; appointment delay (*b* minus *c*), the delay from receiving a request to the patient being offered an appointment; and attendance delay (*c* minus *d*), any delay taking the offered appointment.

The mode of referral from the GP was recorded (mail, fax or telephone), and also any cancellations or non-attenders and the number of visits per patient to diagnosis or discharge. There was no difference in the numbers of clinics or staffing levels in the two intervals. The clinics consisted of one joint breast clinic (one stop, all day) and one single-consultant general surgery clinic per week. After imposition of the directive, 'urgent' referrals were preferentially booked to the joint clinic if an appointment was available within 2 weeks, if not to the general clinic or overbooked to the next joint clinic as a last resort. Delays outside the guidelines were subject to incident reports in 1999. To determine if there was a change in the use of the clinics, a comparison was made of the appointments available and attended between the two intervals, together with the overbookings.

Comparisons were made using the Mann–Whitney U test for non-parametric data and the χ^2 test for contingencies. Significance was accepted at the 5 per cent level and, unless otherwise stated, the data are presented as median (interquartile range). The database was 98 per cent complete.

Results

The number of new patients for the two time intervals increased by 3 per cent from 299 to 308. There was an increase in the number of cancers diagnosed from 24 to 29. This trend mirrored the latest annual new referrals from GPs of 1067 *versus* 1223, a 15 per cent increase in the past 12 months, and breast cancers from 82 to 92.

Assessment of urgency

The assessment of urgency by GPs was incomplete; 58 per cent of all new referrals were 'not specified' in 1998 and this decreased to 49 per cent in 1999. There was a non-significant increase in the frequency of 'urgent' referrals; although probability of cancer may not be the only measure of urgency considered by GPs, overall 57 per cent of the cancers were referred as 'urgent' (14 of 24 in 1998 and 16 of 29 in 1999).

The risk assessment by the breast specialists was 99 per cent complete; 91 per cent of the cancers were selected as 'urgent'. Although not significantly different from the GP 'urgent' group, the probability of a diagnosis of cancer was higher (0·26 *versus* 0·19) (*Table 1*).

Waiting times

There was an increase in the median total delay for all new patients between 1998 and 1999 (13 *versus* 16 days; $P < 0{\cdot}01$). The major part of this was the appointment delay (7 *versus* 9 days; $P < 0{\cdot}001$), which is the delay between receipt of the referral in the breast office and the allocated appointment.

Table 1 Number of patients referred according to risk categories in the two intervals with numbers of cancers diagnosed

		Urgent	Soon	Routine	Not specified
GP referrals					
1998	All	65	5	54	172
	Cancers	14 (0·22)	1 (0·20)	2 (0·04)	7 (0·04)
1999	All	89	11	58	150
	Cancers	16 (0·18)	1 (0·09)	2 (0·03)	10 (0·07)
Specialist category					
1998	All	80	73	144	
	Cancers	21 (0·26)	2 (0·03)	1 (0·01)	
1999	All	104	78	124	
	Cancers	27 (0·26)	0	2 (0·02)	

Values in parentheses are probability of cancer being diagnosed. GP, general practitioner

Table 2 Waiting times for all new, urgent and routine general practitioner referrals in the 3-month intervals in 1998 and 1999

	All new referrals		GP urgent referrals		GP routine referrals	
	1998	1999	1998	1999	1998	1999
Total delay	13 (8–16)	16 (10–22)†	9 (3–14)	10 (5–16)	14 (12–16)	21 (15–29)‡
Referral delay	6 (3–8)	6 (2–8)	1 (0–6)	1 (0–6)	6 (4–7)	7 (6–9)*
Appointment delay	7 (5–8)	9 (6–14)‡	6 (1–7)	7 (2–10)‡	7 (5–9)	13 (8–18)‡
Attendance delay	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)

Values are median (interquartile range). GP, general practitioner. $^{*}P<0{\cdot}05$, $^{\dagger}P<0{\cdot}01$, $^{\ddagger}P<0{\cdot}001$ *versus* 1998 (Mann–Whitney U test)

Table 3 Mode of referral of patients as a determinant of waiting time in the 3-month intervals in 1998 and 1999

	Mail		Fax		Telephone	
	1998	1999	1998	1999	1998	1999
No.	242	234	43	58	7	15†
Total delay (days)	14 (12–19)*	19 (14–26)*†	5 (1–8)	8 (6–12)*†	1 (0–6)	2 (1–5)*
Referral delay (days)	6 (4–8)*	7 (5–9)*	0 (0–2)	0 (0–0)	0 (0–0)	0 (0–0)
Appointment delay (days)	7 (5–8)*	10 (7–15)*†	2 (1–8)	7 (5–10)*†	1 (0–6)	2 (1–2)*

Values are median (interquartile range). For telephone referrals in 1998, the numbers were too small for statistical evaluation. $^{*}P<0{\cdot}01$ *versus* other modes of referral in the same year, $^{\dagger}P<0{\cdot}01$ *versus* 1998 (Mann–Whitney U test)

The total delay was not significantly increased in 1999 for 'urgent' cases (9 *versus* 10 days), although that for 'routine' cases was longer and deteriorated significantly (14 *versus* 21 days; $P<0{\cdot}001$) (*Table 2*).

For patients with a final diagnosis of breast cancer, irrespective of the type of referral, the median total delay (6 days in 1998 and 7 days in 1999) and appointment delay (6 days in 1998 and 7 days in 1999) did not change significantly. There was a non-significant change in the number of GP 'urgent' referrals falling outside the 14-day limit on total delay (ten in 1998 and 29 in 1999). Incident reports revealed most of these to be due to communication problems and involved four patients with breast cancer (median delay 16 (range 15–20) days).

Determinants of delay

The mode of referral significantly affected all types of delay. There was greater use of both fax and telephone in 1999, but this was statistically significant only in the latter (*Table 3*).

Table 4 Clinic details for the 3-month intervals in 1998 and 1999

	1998	1999
Appointments available	851	867
Appointments offered	767	951*
New patients	283	304
Overbookings on clinics	34	109†
Clinic non-attendance	40	74*
Visits per new patient		
Median	1	1*
Mean	1·2 (1·1–1·3)	1·3 (1·3–1·4)

Values in parentheses are 95 per cent confidence intervals of mean. Figures were obtained from clinic records, not as previously from the general practitioner referrals. Overbooking on individual clinics was variable. *$P<0{\cdot}05$, †$P<0{\cdot}001$ *versus* 1998 (χ^2 test)

Despite this change, the total delay increased for all new patients in 1999. The appointments available showed a non-significant increase; one clinic was cancelled in 1998 owing to the audit cycle. In addition, there was a significant increase in clinic overbooking, non-attendance and number of visits to diagnosis or discharge between 1998 and 1999 (*Table 4*).

Discussion

The assessment of urgency in GP referral letters does not necessarily reflect the same thing as the risk categorization made by hospital consultants[7]. GPs often have unique insights and priorities, and these can be useful and illuminating. If the only measure for 'urgent' access is the probability of breast cancer then it would seem that the specialists are currently better placed to make decisions on priority. More serious is that the wait is increased for groups at lower risk (13 per cent of cancers fell outside the hospital guidelines) and, since risk assessment is largely based on age[8], the consequences may be to the detriment of younger women with breast cancer and those with 'soft signs', with amplification of their delays.

The value of the '2 week wait' in terms of psychological or survival advantage in breast cancer has not been addressed. The question is whether guideline-driven GP risk stratification improves access times to a symptomatic breast clinic. Two very similar time intervals were chosen, before and after the NHS directive and without change in the resources available. The conditions and staffing levels pertaining were similar, as was the mode of data acquisition. There was no change for patients with breast cancer, but overall clinic access times were significantly longer.

As a consequence of HSC 1998/242, the delays to 'urgent' cases are audited nationally, but these patients constituted only 25 per cent of the authors' new GP referrals and fewer still when considered in the context of cases from all sources. The guidelines for 'urgent' referral could be modified (e.g. by decreasing the age limits) to include more patients with cancer, but it will not be possible to be completely sensitive. Furthermore, the effect of delay on excluded patients, particularly their anxiety before knowing the diagnosis, has not been considered. Consequently a broader measure of the median wait for all referrals gives a clearer picture of the service.

Communication with the specialist clinic, defined as the referral delay, included not only the time taken by the GP but also by the hospital systems. This can be minimized with the use of telephonic communication (*Table 3*), which also produces significant improvements in the appointment delay, partly because the intimacy of the contact encouraged appointments to be made immediately in many cases.

The availability of one-stop clinics is limited and patients with suspected breast cancer are best seen in these clinics. Pressure to reduce waiting times in the absence of increased resources was accommodated by increasing the density of bookings or by moving patients to non-specialist clinics. In terms of the Patients Charter (30-min wait) and the British Association of Surgical Oncology guidelines[9], both should be discouraged. Faced with these alternatives the tendency has been to overbook, in the belief that the anxiety induced by delay in getting an appointment is greater than that of the wait in clinic[10]. The increase in the number of revisits may be a consequence of the use of non-dedicated clinics to accommodate the '2 week wait'.

The number of new breast referrals has increased a little. However, appointment numbers have increased substantially as a result of revisits, breast cancer follow-up and (possibly) a wave of conservatism, resulting in increasing pressure on the clinics. Non-attendance has also increased and, since most of these patients are given a further appointment, the required number of appointment slots has increased. The causes of non-attendance are unclear; there may be a convenience factor since re-appointment is easy. Perhaps the rapidity of appointment is a problem for certain patients owing to social and domestic imperatives.

In conclusion, breast specialists currently seem better placed to assess the risk of breast cancer from a referral letter if this is to be the determinant of the urgency of a clinic appointment. The wait to be seen in a specialist breast clinic results mainly from delay in the hospital systems arranging appointments and telephonic communication with the GPs could improve this. Access times for patients with breast cancer have not changed in this hospital but, in the absence of extra resources, waiting times are increased for those referred routinely owing to overloading of the system.

Acknowledgements

The authors thank Mr B. J. Harrison (Northern General Hospital) who critically reviewed the manuscript, and Miss A. Thackeray and Mrs J. Brummitt for coordinating data collection.

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Original article

Cholecystectomy, peptic ulcer disease and the risk of adenocarcinoma of the oesophagus and gastric cardia

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Background: Gastro-oesophageal reflux is a strong risk factor for oesophageal adenocarcinoma. Bile and pancreatic enzymes may be particularly carcinogenic. Cholecystectomy causes an increased gastric level of these constituents. A decreased risk of oesophageal adenocarcinoma has been observed in persons infected with cagA-positive *Helicobacter pylori*. There is a strong correlation between ulcer disease and *Helicobacter pylori* infection. The aim of this study was to determine whether previous cholecystectomy or peptic ulcer disease affects the risk of oesophageal carcinoma.

Methods: Data were collected as a nationwide population-based case–control study in Sweden between 1995 and 1997. Multivariate adjusted odds ratios (ORs) were calculated with logistic regression.

Results: There was no statistically significant association between cholecystectomy and the risk of oesophageal carcinoma. Among persons with previous peptic ulcer, the adjusted OR for oesophageal adenocarcinoma was below unity (OR = 0·6, 95 per cent confidence interval 0·3–1·1). The relative risk estimates for cardia adenocarcinoma and oesophageal squamous cell carcinoma were close to unity.

Conclusion: Cholecystectomy, despite its effect on the composition of gastric juice, does not appear to increase the risk of adenocarcinoma of the oesophagus or gastric cardia. While the data do not contradict a protective effect of *H. pylori*, the results are also consistent with absence of such an effect.

Paper accepted 24 January 2000

British Journal of Surgery 2000, **87**, 1087–1093

Introduction

The incidence of oesophageal adenocarcinoma has increased rapidly over the past three decades in the Western world[1–3]. The reasons are not understood. As gastro-oesophageal reflux is a strong risk factor[4], luminal factors may play an important role in the aetiology. Several studies have shown a correlation between the severity of gastro-oesophageal reflux disease and the amount of duodenogastro-oesophageal reflux[5–7]. Bile and pancreatic enzymes have cytotoxic effects on the oesophageal mucosa[8,9]. In animal studies, refluxing bile and pancreatic juice have been found to be carcinogenic to the oesophageal mucosa[10–13]. After cholecystectomy there is a change in the gastric milieu with an increased intragastric concentration of bile[14]. Another effect of cholecystectomy is an increase in the prevalence of gastro-oesophageal reflux disease of about 35–50 per cent[15–19]. The first hypothesis in this study is that following cholecystectomy patients are at an increased risk of developing oesophageal adenocarcinoma.

A reduced risk of oesophageal cancer has been observed in patients infected with *Helicobacter pylori*, possibly because atrophic gastritis results in reduced gastric secretion, thereby alleviating gastro-oesophageal reflux[20,21]. The second hypothesis is that peptic ulcer disease, caused mainly by infection with *H. pylori*, could 'protect' against carcinogenesis in the oesophagus.

Patients and methods

Patients

The study included four separate groups of patients. Group 1 comprised 189 patients with adenocarcinoma of the oesophagus. In group 2 there were 262 patients with adenocarcinoma of the gastric cardia. In group 3 there were 167 with squamous cell carcinoma of the oesophagus. Group 4 consisted of 820 control subjects. Groups 1 and 2 together constituted 85 per cent of all eligible patients with adenocarcinoma in Sweden during the study period. The participation rate in groups 3 and 4 was 73 per cent.

Design

The methodology of this population-based nationwide case–control study has been described in detail elsewhere[4]. In brief, the study base was the entire population of Sweden under 80 years of age, born in Sweden and still residing there between 1 December 1994 and 31 December 1997. All incident cases of oesophageal and gastric cardia adenocarcinoma and half the incident cases of oesophageal squamous cell carcinoma (subjects born on even dates) were eligible. A comprehensive organization for rapid case ascertainment, with contact persons at all 195 departments of general surgery, thoracic surgery, otorhinolaryngology, oncology and pathology in Sweden, as well as continuous collaboration with the six regional tumour registries, ensured that every case throughout the country was identified shortly after diagnosis.

Control subjects were randomly selected from 10-year age and sex strata in the entire Swedish population, using the continuously updated computerized population register. The numbers selected in each stratum were adjusted to mimic the age and sex distribution among patients with oesophageal adenocarcinoma.

Tumour classification

To reduce tumour misclassification, uniform protocols for documentation of the tumours were introduced at the participating departments. The distance between the gastro-oesophageal junction and the upper and lower borders of the tumour were measured endoscopically. Serial biopsies were taken along the oesophagus and gastro-oesophageal junction. Surgeons and pathologists gave standardized, detailed descriptions of the location of the cancer in resected cases. Finally, the biopsies and/or surgical specimens from 97 per cent of cases were reviewed by one pathologist. A cancer of the gastric cardia had to have its centre within 2-cm oral, or 3 cm aboral to the gastro-oesophageal junction. If Barrett's oesophagus was detected adjacent to the tumour, it was classified as oesophageal.

Exposure information

All patients and controls underwent computer-aided face-to-face interviews by specially trained, professional interviewers shortly after diagnosis. Questions were asked about a history of cholecystectomy and the date for surgery. Information about previous peptic ulcer, its location, and the date for diagnosis, as recalled by the patient, was also collected. It was not possible to search the medical records of each patient to confirm the diagnosis. Ulcers that were first detected within 5 years of the interview were disregarded. Information was gathered concerning several potential confounding factors that were adjusted for in the multivariate analysis: age (in 5-year classes), sex, reflux symptoms (occurrence of reflux was defined as reflux symptoms occurring at least once a week over a period of 6 months or more), educational level (in three classes), body mass index (in quartiles), tobacco use (tobacco smoking status 2 years before the interview was classified into never smoked, previous smoker and current smoker of cigarettes, cigars and pipes), alcohol use (total amount of pure alcohol from all types of alcoholic beverages in four classes), intake of fruit and vegetables (total consumption in three classes), meal size (reported by indicating the sizes of seven common dishes in a picture guide and classified into three levels) and physical activity (physical activities both at work and during leisure time were combined into four levels of activity).

Statistical analysis

Logistic regression was used in both univariate and multivariate modelling. Model parameters were estimated by the maximum likelihood method[22]. From these estimates, odds ratios (ORs) with 95 per cent confidence intervals (c.i.) were calculated. In the baseline model, adjustments were made for age and sex, as the frequency distribution of these factors was not necessarily the same in different groups. In the multivariate modelling, adjustments were further made for the nine potential confounding variables. In one model, reflux symptoms were excluded in the analysis.

Ethical considerations

Individual informed consent was obtained before the interview, and the study was approved by all regional ethics committees in Sweden.

Results

Cholecystectomy

There was no statistically significant association between cholecystectomy and any of the three cancers studied (*Table 1*). Among persons who had had cholecystectomy, the adjusted OR for oesophageal adenocarcinoma, cardia adenocarcinoma and oesophageal squamous cell carcinoma was 1·0 (95 per cent c.i. 0·6–1·7), 0·7 (0·4–1·1) and 0·8 (0·4–1·5) respectively, compared with persons who had had no such surgery. There was no increased risk with increasing latency between operation and cancer occurrence. If anything, there was a trend towards a decreased risk of cardia adenocarcinoma following cholecystectomy. An analysis was also made concerning the cancer risk among persons

Table 1 Risk of oesophageal adenocarcinoma, gastric cardia adenocarcinoma and squamous cell carcinoma in patients with and without a history of cholecystectomy

		Oesophageal adenocarcinoma			Gastric cardia adenocarcinoma			Oesophageal squamous cell carcinoma		
	No. of controls	No. of cases	OR adjusted for age and sex	Multivariate adjusted OR	No. of cases	OR adjusted for age and sex	Multivariate adjusted OR	No. of cases	OR adjusted for age and sex	Multivariate adjusted OR
No cholecystectomy	728	162	1·00	1·00	241	1·00	1·00	150	1·00	1·00
Time of cholecystectomy before cancer diagnosis (years)										
<5	18	5	1·19	0·86	6	1·04	0·87	4	1·04	1·24
			(0·43–3·27)	(0·29–2·50)		(0·40–2·65)	(0·32–2·35)		(0·34–3·20)	(0·37–4·14)
5–10	18	8	2·16	1·44	4	0·70	0·60	3	0·79	0·85
			(0·91–5·11)	(0·58–3·57)		(0·23–2·11)	(0·19–1·88)		(0·22–2·78)	(0·20–3·71)
>10	56	14	1·12	0·95	11	0·63	0·62	10	0·70	0·70
			(0·60–2·08)	(0·50–1·82)		(0·32–1·24)	(0·31–1·24)		(0·34–1·43)	(0·31–1·54)
Total	92	27	1·32	1·03	21	0·73	0·67	17	0·78	0·82
			(0·83–2·12)	(0·63–1·69)		(0·44–1·20)	(0·39–1·13)		(0·44–1·36)	(0·43–1·54)

Values in parentheses are 95 per cent confidence intervals. OR, odds ratio; multivariate analysis included adjustment for age, sex, tobacco use, alcohol use, body mass index, educational level, intake of fruit and vegetables, meal size and physical activity

Table 2 Risk of oesophageal adenocarcinoma, gastric cardia adenocarcinoma and squamous cell carcinoma in patients with a history of cholecystectomy, with and without concomitant reflux, and in those without a history of cholecystectomy or reflux

		Oesophageal adenocarcinoma			Gastric cardia adenocarcinoma			Oesophageal squamous cell carcinoma		
	No. of controls	No. of cases	OR adjusted for age and sex	Multivariate adjusted OR	No. of cases	OR adjusted for age and sex	Multivariate adjusted OR	No. of cases	OR adjusted for age and sex	Multivariate adjusted OR
No cholecystectomy or reflux	618	67	1·00	1·00	172	1·00	1·00	128	1·00	1·00
Reflux, no cholecystectomy	110	95	7·97	8·23	69	1·09	1·33	22	2·21	2·21
			(5·46–11·8)	(5·43–11·8)		(0·66–1·81)	(0·76–2·34)		(1·56–3·14)	(1·52–3·21)
Cholecystectomy, no reflux	67	9	1·25	0·97	15	0·89	0·97	14	0·84	0·77
			(0·59–2·63)	(0·45–2·10)		(0·48–1·66)	(0·48–1·95)		(0·46–1·51)	(0·42–1·43)
Cholecystectomy and reflux	25	18	6·54	5·19	6	0·51	0·53	3	0·89	0·83
			(3·36–12·7)	(2·52–10·7)		(0·15–1·74)	(0·14–2·10)		(0·36–2·23)	(0·32–2·15)

Values in parentheses are 95 per cent confidence intervals. OR, odds ratio; multivariate analysis included adjustment for age, sex, tobacco use, alcohol use, body mass index, educational level, intake of fruit and vegetables, meal size and physical activity

with the combination of oesophageal reflux symptoms and previous cholecystectomy. Although based on small numbers of observed cases, cholecystectomy did not seem to add further to the positive association between gastro-oesophageal reflux disease and oesophageal adenocarcinoma (*Table 2*). In the 118 subjects with Barrett's oesophagus, of whom 14 had had a cholecystectomy, there was no increased risk of oesophageal adenocarcinoma (data not shown).

Peptic ulcer disease

In the simple age- and sex-adjusted analyses, there were no conspicuous and statistically significant associations between self-reported previous ulcer disease and risk of any of the studied tumours (*Table 3*). All ulcers were not classified as either duodenal or gastric, which accounts for the missing four patients in group 3. After adjustments, however, the OR for oesophageal adenocarcinoma among individuals with a peptic ulcer history was 0·6 relative to persons without such a history. This departure from unity was not statistically significant (95 per cent c.i. 0·3–1·1). The risk deficit was of similar magnitude regardless of whether the ulcer had a gastric or duodenal location. Reflux was the covariate that accounted for most of the confounding. The corresponding relative risk estimates for adenocarcinoma of the gastric cardia and oesophageal squamous cell carcinoma were close to unity.

Table 3 Risk of oesophageal adenocarcinoma, gastric cardia adenocarcinoma and squamous cell carcinoma in patients with a history of gastric or duodenal ulcer and in those with no such history

		Oesophageal adenocarcinoma			Gastric cardia adenocarcinoma			Oesophageal squamous cell carcinoma		
	No. of controls	No. of cases	OR adjusted for age and sex	Multivariate adjusted OR	No. of cases	OR adjusted for age and sex	Multivariate adjusted OR	No. of cases	OR adjusted for age and sex	Multivariate adjusted OR
No ulcer	737	168	1·00	1·00	235	1·00	1·00	150	1·00	1·00
History of ulcer										
Duodenal	63	10	1·06 (0·48–2·34)	0·64 (0·27–1·52)	11	0·84 (0·40–1·76)	0·71 (0·33–1·51)	6	0·73 (0·27–1·97)	0·71 (0·26–1·90)
Gastric	76	11	0·97 (0·46–2·02)	0·66 (0·30–1·46)	16	1·18 (0·63–2·22)	0·96 (0·51–1·84)	7	0·80 (0·32–1·96)	0·77 (0·31–1·91)
Total	83	21	0·97 (0·56–1·68)	0·58 (0·32–1·07)	27	0·95 (0·58–1·55)	0·78 (0·47–1·3)	17	0·88 (0·47–1·64)	0·85 (0·45–1·60)

Values in parentheses are 95 per cent confidence intervals. OR, odds ratio; multivariate analysis included adjustment for age, sex, occurrence of reflux symptoms, tobacco use, alcohol use, body mass index, educational level, intake of fruit and vegetables, meal size and physical activity

Discussion

In this study cholecystectomy was not found to increase the risk of adenocarcinoma of the oesophagus or gastric cardia, despite the increase in allegedly carcinogenic components of the gastric juice[23], either overall or among persons with oesophageal reflux. Although there were some indications that patients with a previous history of peptic ulcer might have a lower than expected risk of oesophageal adenocarcinoma after adjustment for reflux occurrence, this seemingly protective effect was also consistent with a chance finding.

This study is, to the authors' knowledge, the first to examine an association between cholecystectomy and risk of oesophageal adenocarcinoma in humans. There have been good reasons for suspecting a positive association. Gastro-oesophageal reflux is a strong risk factor for gastro-oesophageal adenocarcinoma[4], and a previous history of cholecystectomy has been shown to be associated with an increased prevalence of such reflux[16,19,24]. Moreover, cholecystectomy increases duodenogastric reflux[14,15,18,25]. Components of bile and pancreatic juice cause pH-dependent oesophageal damage in animal studies[8,9], and clinical observations indicate that patients with concomitant gastro-oesophageal and duodenogastric reflux have more severe oesophagitis than those with gastro-oesophageal reflux alone[5–7]. More than half of the patients with Barrett's oesophagus, a clearly premalignant complication of gastro-oesophageal reflux[26], have significant duodenogastric reflux[27–32]. In the rat, gastric juice mixed with duodenal juice, but not gastric juice alone, enhances 2,6-dimethylnitrosomorpholine-induced oesophageal carcinogenesis[12]. The findings of the present study, however, seem to contradict the previous suspicion[4] that admixture of duodenal contents plays an important role in reflux-associated oesophageal adenocarcinoma in humans. At least, the risk associated with cholecystectomy is unlikely to come even near the risk linked to gastro-oesophageal reflux. This seems to imply that acid is, in fact, the culprit. However, further studies on the association between adenocarcinoma of the oesophagus and bile reflux are warranted because of the small number of cholecystectomies in this study.

This study does not provide strong support for the recently reported negative association between infection with cagA-positive *H. pylori* and adenocarcinoma of the oesophagus and/or gastric cardia[33], nor is such a relationship clearly refuted. The mechanisms behind this seemingly protective effect have remained elusive, but speculations tend to attribute it to the atrophy and hypochlorhydria that sometimes develop[21,34–37], particularly in persons harbouring cagA-positive strains[36]. If this hypothesis is correct, then gastric acid, rather than duodenal juice, is again implicated. The details of the relationship between *H. pylori* infection and gastro-oesophageal reflux are not yet clearly established, but no clear association has so far emerged[38,39]. Hence, the protection against oesophageal adenocarcinoma is expected to be found only in patients with *H. pylori*-induced atrophy and hypochlorhydria. Such hypochlorhydria is common in patients with gastric ulcer but not in those with duodenal ulcer. The similar tendency towards the low risk, albeit not statistically significant, found in this study in patients with gastric and duodenal ulcer is not consistent with expectations, and may indicate a bogus finding. As information about non-steroidal anti-inflammatory drug use was lacking, negative confounding by this factor, positively associated with gastric ulcer[40] and reportedly protective against oesophageal adenocarcinoma[41,42], may have contributed further to the tendency towards an inverse association between gastric ulcer and oesophageal adenocarcinoma.

The strengths of this study are the population-based design, the complete case ascertainment and comparably high participation rate, the uniform and thorough classification of all tumours, and the comprehensive computer-aided interviews that enabled adjustment for conceivable confounding factors. There are also important caveats concerning the conclusions reached here. Non-differential misclassification of the exposure among cases and controls may have led to underestimation of any associations, although recall bias is inconceivable as an explanation for the absence of association between cholecystectomy and cancer risk, and the tendency towards low risk of oesophageal adenocarcinoma in patients with a peptic ulcer history. While the recollection of previous major surgery is usually adequate, misclassification of peptic ulcer could be substantial. Persons with peptic ulcer may have remained undiagnosed, and patients with non-ulcer dyspepsia may believe that they have had ulcer disease. Given that dyspepsia is often managed with a minimum of investigation[43], review of case records, if at all feasible, would probably be of limited help. The absence of any differences in risk among individuals with duodenal and gastric ulcer should be interpreted cautiously and may mainly reflect misclassification of ulcer site. To complicate the interpretation further, symptoms of peptic ulcer could have been mixed up with reflux symptoms, strongly associated with risk, and vice versa. If it is assumed that the number of previous healthcare contacts is positively associated with the propensity for participation in the study, the lower participation rate among the control subjects may have resulted in a selective loss of controls who had not undergone cholecystectomy and who had not been given a diagnosis of ulcer. The resulting overestimation of the exposure prevalence among controls could have contributed to the somewhat lower relative risk estimates, possibly cancelling a weak positive association between cholecystectomy and oesophageal adenocarcinoma risk, and exaggerating the seemingly protective effect of peptic ulcer. Moreover, notwithstanding the fact that the study comprised all adenocarcinoma cases that occurred during 3 years in the whole of Sweden, the precision of estimates is no more than moderate. The 95 per cent confidence intervals indicate that the true risk of adenocarcinoma in cholecystectomized patients could be increased by as much as 70 per cent compared with the risk in non-cholecystectomized persons, and the risk in patients with a history of peptic ulcer could be 70 per cent lower than that in ulcer-free individuals.

In conclusion, this study provides indirect indications that gastric acid, not duodenal juice, is an important factor in reflux-associated oesophageal adenocarcinoma. Further studies might, however, still be warranted. This information might be useful if preventive measures, directed against the reflux, were to be considered. The relationship between *H. pylori* infection and risk of adenocarcinoma of the oesophagus and gastric cardia clearly requires further study.

Acknowledgements

The authors are grateful to Leila Nyrén for invaluable coordination of the fieldwork and to Anders Lindgren for expert pathology review. They also thank Drs Lars Backman and Lars Granström from the Department of Surgery at Danderyd Hospital, and all the 227 doctors who acted as contact persons at the participating departments and/or provided invaluable input during the planning of this study.

This work was supported by the National Cancer Institute (grant R01 CA57947–03), the Swedish Cancer Society (ON), the Dalarna Research Institute and the Swedish Medical Research Council (no. 13150).

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Original article

Role of xanthine oxidase in small bowel mucosal dysfunction after surgical stress

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Background: The small intestine is highly susceptible to surgical stress even at remote locations. An earlier study using a rat model indicated that oxidative stress plays an important role in this process. The enzyme xanthine oxidase is an important source of free radicals in the small intestine. The role of this enzyme in intestinal damage after surgical stress was examined.

Methods: Rats pretreated with xanthine oxidase inhibitors were subjected to surgical stress by opening the abdomen and handling the intestine, as done during laparotomy. Enterocytes at various stages of differentiation were isolated and the protection offered by xanthine oxidase inhibitors against damage due to surgical stress was determined and compared with normal controls. Protection against ultrastructural changes to the mucosa, as well as mitochondrial function was examined.

Results: Surgical stress affected both the villus as well as crypt cells, causing increased superoxide generation, accompanied by increased activity of xanthine oxidase. Xanthine oxidase inhibitors ameliorated the increased superoxide generation, and protected against mitochondrial damage and ultrastructural changes in the intestine.

Conclusion: Surgical stress affects both the villus and crypt cell populations in the small intestine. The enzyme xanthine oxidase maybe an important mediator of surgical stress in the intestine.

Paper accepted 5 February 2000

British Journal of Surgery 2000, 87, 1094–1101

Introduction

Surgical stress affects a number of different organ systems throughout the body[1]. A major damaging effect of surgical stress is on the intestine, which is highly susceptible even after surgery at remote locations[2]. Surgical stress increases intestinal permeability and induces bacterial translocation into the systemic circulation[3], which has been implicated in the multiple organ failure syndrome[4]. The intestinal mucosa consists of differentiated absorptive cells that originate in the crypt. The crypt stem cells proliferate to produce the epithelial cells that migrate upwards and undergo differentiation as they reach the villus[5]. Thus the intestinal epithelium contains cells at various stages of differentiation. The time taken for this process varies between species, but is about 3 days. Any damage to the proliferating crypt cells or the differentiated villus cells may affect either process, leading to altered cell populations and functional derangement in the intestine. An earlier study from this laboratory indicated that laparotomy with mild intestinal handling, as could occur during any abdominal surgery, can result in oxidative stress in the enterocyte[6]. This damage is maximal 60 min after stress and is probably mediated by increased activity of the superoxide generating enzyme, xanthine oxidase, accompanied by mitochondrial dysfunction. The damage is reversible and, by 24 h after stress, most of the parameters returned to normal levels.

To understand more about the mechanism of damage to the enterocyte and its reversibility, the present study was undertaken to investigate the response of the different cell populations in rat small intestine to surgical stress after mild handling. The aim was also to determine the contribution of the superoxide generating enzyme, xanthine oxidase, to cell damage in this model of surgical stress.

Materials and methods

3-(4,5 Dimethylthiazol-2-yl),2,5-diphenyl tetrazolium bromide (MTT), MTT formazan, dimethyl sulphoxide, xanthine, adenosine 5′-diphosphate (ADP), succinate, ethylene glycol-bis(β-aminoethyl ether)-N,N,N′,N′-tetra-acetic acid (EGTA), dithiothreitol, Hepes and bovine serum albumin (BSA) were obtained from Sigma

Chemical, St. Louis, MO, USA. All other chemicals and solvents used were of analytical grade.

Animals

Adult Wistar rats of both sexes (200–250 g), exposed to a daily 12-h light–dark cycle and fed water and rat chow *ad libitum*, were used for the study. The rats were randomly divided into four groups ($n = 8$): control (no operation), surgical stress (intestinal handling), allopurinol (surgical stress after allopurinol pretreatment) and sodium tungstate (surgical stress after sodium tungstate pretreatment) groups. This study was cleared by the Institutional Animal Experimentation Ethics Committee.

Induction of surgical stress

Overnight fasted rats were anaesthetized by ketamine injection (50 mg/kg body-weight) and the abdominal wall was opened by a vertical incision of approximately 4 cm. The intestine was then gently moved and the ileocaecal junction identified. The intestine was then handled along its entire length from the ileocaecal junction proximally, simulating the 'inspection' that occurs in a clinical setting. The intestine was then replaced in the abdominal cavity. The whole process was completed within 1–2 min. The abdominal wall was then repaired and the animals were allowed to recover from anaesthesia. The animals were killed by decapitation either at 60 min or 24 h after the surgical procedure. Control rats were injected with ketamine and killed by decapitation without opening the abdominal wall. Control rats were also included in allopurinol- and tungstate-treated groups.

The intestine from control and surgically treated rats was removed for the study of various cell populations. Enterocytes at various stages of maturation were isolated into separate fractions as described previously using the metal chelation method[7]. The cell fractions at various levels were numbered 1–9, fraction 1 being villus tip cells, fraction 9 being crypt stem cells and the middle fractions (8–2) containing cells with progressively increasing differentiation. For studies using mitochondria, total enterocytes were obtained from the intestine and mitochondria were isolated from the enterocytes as described previously[8].

Inhibition of xanthine oxidase activity

Xanthine oxidase was inhibited by treatment of the animals with either allopurinol or sodium tungstate. Rats were given an intraperitoneal injection of allopurinol 100 mg/kg body-weight 1 h before laparotomy or were fed sodium tungstate (0·7 g per kg body-weight) in drinking water for 5 days before surgery.

Assays

Superoxide generation was assessed by dye reduction, using the tetrazolium dye MTT that is reduced by superoxide radicals. The MTT assay was performed on the cell suspension or mitochondria using a microplate reader as described before[9]. Xanthine oxidase was measured using a spectrophotometric assay based on the production of uric acid, which is measured at 295 nm[10]. Protein was measured using bovine serum albumin as standard[11].

Mitochondrial function

Oxygen uptake was determined polarographically using a Clark type electrode in 2 ml respiratory medium (sucrose 225 mmol/l, magnesium chloride 5 mmol/l, monopotassium phosphate 10 mmol/l, potssium chloride 20 mmol/l, Tris 10 mmol/l and Hepes 5 mmol/l, pH 7·4) containing succinate 5 mmol/l as respiratory substrate. A mitochondrial protein of concentration of 2 mg/ml was used. Oxygen uptake was stimulated with ADP 0·3 mmol/l. Swelling of control and surgically stressed mitochondria was determined by the decrease in absorbance at 540 nm up to 10 min[12].

Histological studies

Mucosal tissues from control rats and those obtained at 60 min and 24 h after surgical stress, with and without pretreatment with xanthine oxidase inhibitors, were fixed in 2·5 per cent glutaraldehyde, post fixed in osmium tetroxide and embedded in epoxy resin. Sections 1 µm thick were cut and stained with toluidine blue. Suitable areas for ultrastructural study were chosen after examining the 1-µm sections under the light microscope.

For ultrastructural study, ultrathin sections were cut on an LKB UM4 ultramicrotome with a diamond knife (Diatome, Biel, Switzerland). The sections were mounted on copper grids and stained with uranyl acetate and lead citrate. The grids were examined under a Philips EM201C electron microscope (Philips, Eindhoven, The Netherlands)

Statistical analysis

Data are expressed as mean(s.d.). Statistical analysis was performed with Student *t* test.

Results

Superoxide generation

The intestinal epithelium undergoes a continuous turnover and the cells along the villus–crypt axis are thus at various stages of differentiation. To determine whether cells from any particular population are more susceptible to surgical stress-mediated injury, cells were isolated from villus, middle and crypt fractions, and assayed for superoxide production using MTT reduction at different time intervals after surgical stress in comparison to control cells (*Fig. 1*). There was progressive MTT reduction 60 min after stress seen throughout the intestinal villus–crypt axis. By 24 h after stress, levels had returned close to control values in most of the fractions.

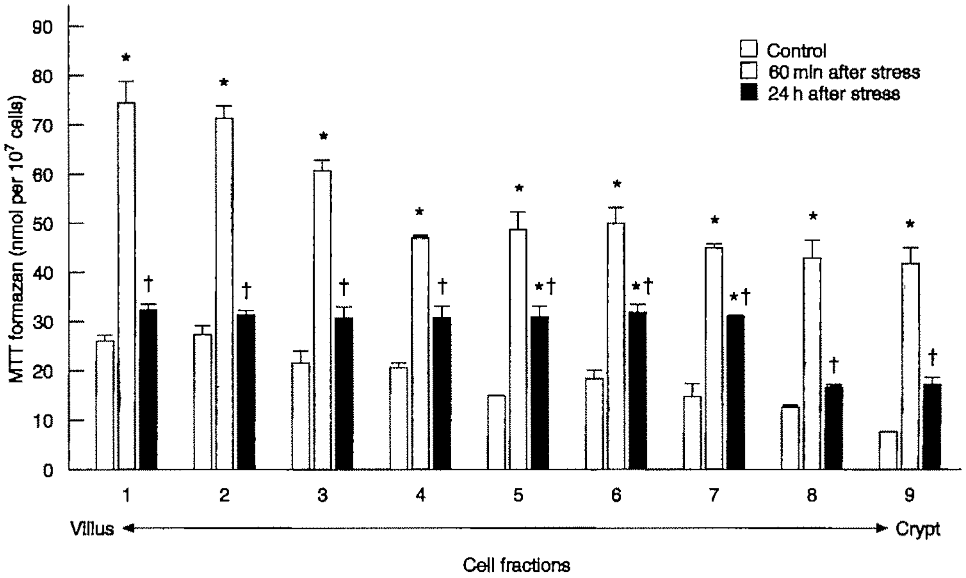

Fig. 1 Superoxide generation measured by 3-(4,5 dimethylthiazol-2-yl),2,5-diphenyl tetrazolium bromide (MTT) reduction in various cell fractions from the villus–crypt axis in rat intestine after surgical stress. Values are mean(s.d.) from three separate experiments. *$P < 0{\cdot}05$ *versus* control, †$P < 0{\cdot}05$ *versus* 60 min (Student *t* test)

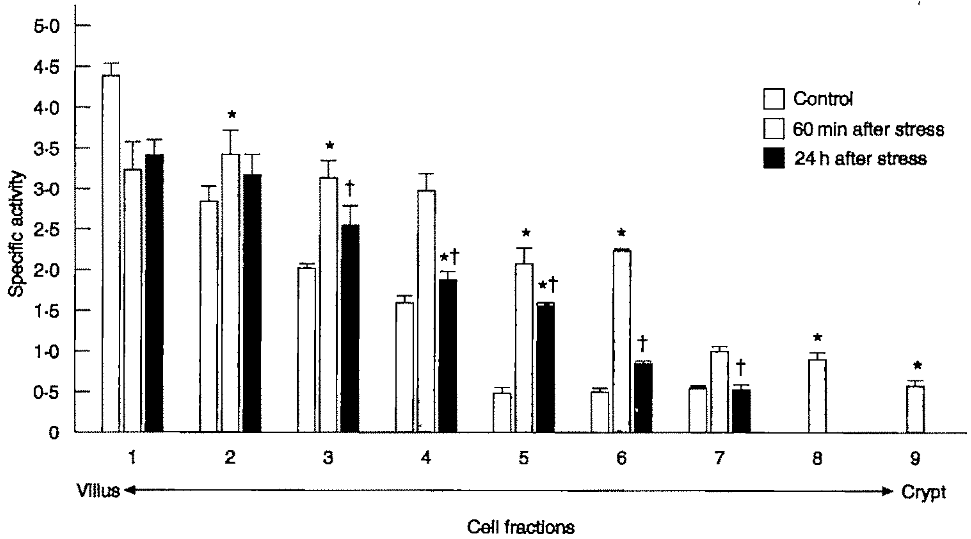

Fig. 2 Xanthine oxidase activity in various cell fractions from the villus–crypt axis in rat intestine after surgical stress. Values are mean(s.d.) from three separate experiments. *$P < 0{\cdot}05$ *versus* control, †$P < 0{\cdot}05$ *versus* 60 min (Student *t* test)

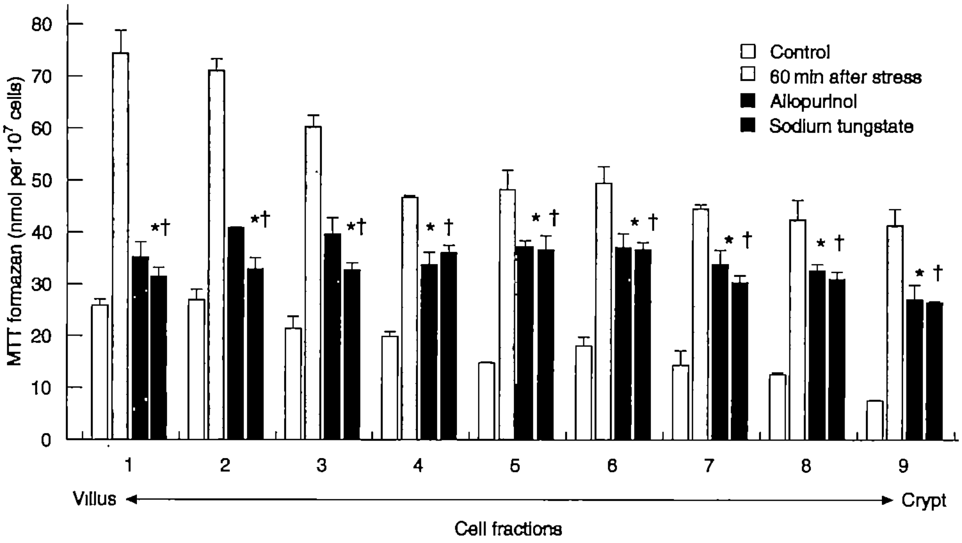

Fig. 3 Superoxide generation measured by 3-(4,5 dimethylthiazol-2-yl),2,5-diphenyl tetrazolium bromide (MTT) reduction in various cell fractions from the villus– crypt axis in rat intestine 60 min after surgical stress in rats pretreated with xanthine oxidase inhibitors or controls. Values are mean(s.d.) from three separate experiments. *$P < 0{\cdot}05$ *versus* 60 min after stress, †$P < 0{\cdot}05$ *versus* control (Student *t* test)

Xanthine oxidase activity

An earlier study using isolated total enterocytes demonstrated an increased activity of xanthine oxidase after surgical stress[6]. In the present study xanthine oxidase was assayed in various enterocyte populations separately, to determine whether the increased activity was confined to any particular cell population of the mucosa. The increase in xanthine oxidase activity after stress was most marked in the middle and crypt fractions. This activity returned to the control level by 24 h after surgical stress (*Fig. 2*). The intestinal crypt cells had no detectable xanthine oxidase activity in control rats or 24 h after surgical stress. Activity was detectable 60 min after stress in treated rats, although the activity was lower than that in villus cells.

Xanthine oxidase activity causes generation of free radicals and oxidative stress, which was maximal 60 min after surgical stress using the present model. Therefore superoxide generation measured using MTT reduction was assessed in xanthine oxidase-deficient animals and controls in the various cell fractions (*Fig. 3*). Pretreatment of animals with the xanthine oxidase inhibitors allopurinol or sodium tungstate protected against the increased MTT reduction by isolated enterocytes after surgical stress. This protection was more evident in villus cells than middle or crypt cells. No xanthine oxidase activity could be detected in any cell fractions from xanthine oxidase inhibited (allopurinol or sodium tungstate) animals (data not shown).

Mitochondrial function

It has previously been observed by the authors that surgical stress results in enterocyte mitochondrial dysfunction due to uncoupling of mitochondria (R. Anup, P. Susama and K. A. Balasubramanian, unpublished observation). To determine whether pretreatment with xanthine oxidase inhibitors could protect against this, MTT reduction was assayed using mitochondria isolated 60 min after stress in rats treated with allopurinol or sodium tungstate (*Fig. 4a*). Inhibition of xanthine oxidase activity prevented the increase in MTT reduction caused by surgical stress. In addition, uncoupling of respiration, determined by the fall in mitochondrial respiratory control ratio, seen 60 min after surgical stress, was prevented by xanthine oxidase inhibition (*Fig. 4b*). Another characteristic feature of mitochondrial damage, mitochondrial swelling, was also prevented by xanthine oxidase inhibition (*Fig. 4c*).

Histological changes

An earlier study from this laboratory demonstrated ultrastructural changes in the intestinal mucosa following surgical stress, resulting in widening of the intercellular spaces, most prominent at 60 min after intestinal handling[6]. To complement the biochemical studies, histological studies were carried out in the present study to determine whether inhibition of xanthine oxidase could prevent the ultrastructural changes due to surgical stress. On light

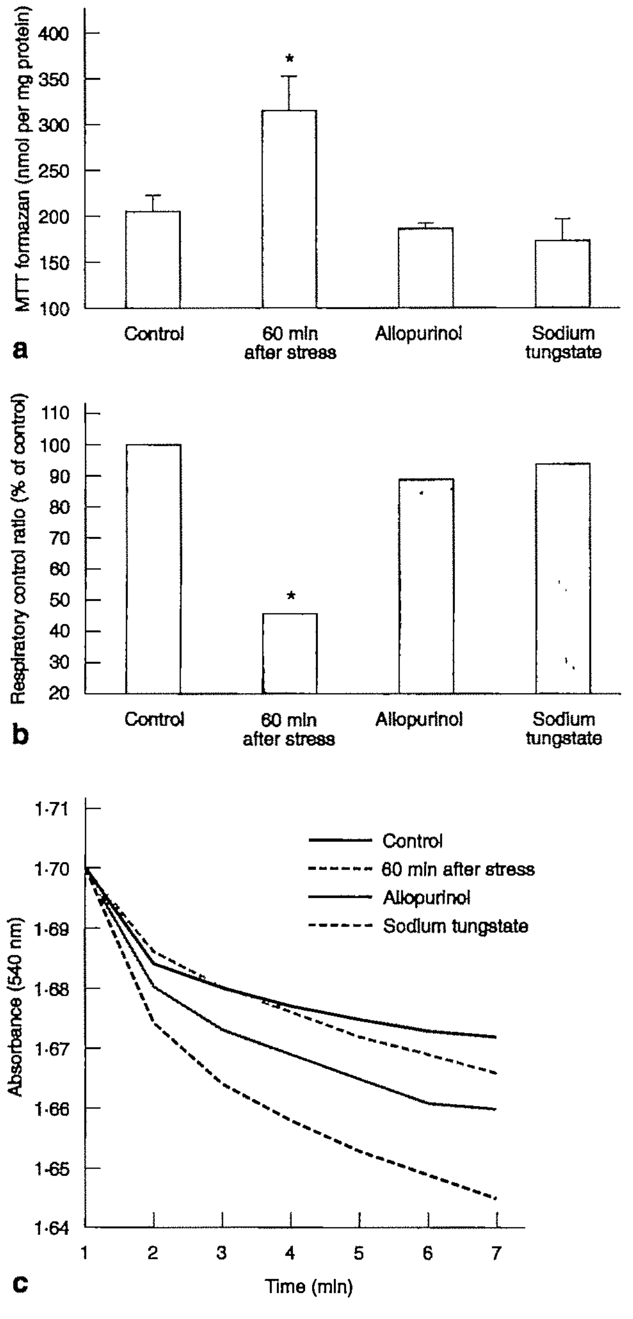

Fig. 4 Mitochondrial function after surgical stress. **a** 3-(4,5 Dimethylthiazol-2-yl),2,5-diphenyl tetrazolium bromide (MTT) reduction and **b** respiratory control ratio in mitochondria isolated from enterocytes 60 min after surgical stress in rats pretreated with xanthine oxidase inhibitors or controls. Values are mean(s.d.) from three separate experiments. **c** A representative trace of mitochondrial swelling in rat enterocytes isolated following surgical stress, in the presence and absence of xanthine oxidase inhibitors. $^*P < 0{\cdot}05$ *versus* control (Student t test)

microscopic examination, rats subjected to surgical stress showed mild patchy widening of intercellular spaces of the villus epithelium and focal oedema with vasodilatation of the lamina propria (*Fig. 5*). The changes were reduced or absent in samples obtained from rats pretreated with xanthine oxidase inhibitors. On ultrastructural examination (*Fig. 6*), mucosa subjected to surgical stress showed widening of the intercellular spaces of adjacent epithelial cells over the villi. The widening was more prominent at the basal aspect with altered gap junctions. Control groups did not display any such changes. At 24 h after surgical stress, these changes were absent or extremely focal. The changes were less marked among animals pretreated with allopurinol or sodium tungstate, in which the intercellular widening was reduced by 50 and 68 per cent respectively.

Discussion

The intestine is highly susceptible to surgery, even at remote locations, and an earlier study using a rat model indicated that handling of the intestine following laparotomy caused oxidative stress in the enterocyte, accompanied by functional alterations in the intestine[6]. Since the intestinal epithelium consists of cells at various stages of differentiation[5], it was of interest to determine whether the damage caused by surgical stress was confined to a particular cell population of the epithelium or was widespread. In the present study there was increased MTT reduction, 60 min after surgical stress, throughout the cells of the villus–crypt axis. The tetrazolium dye MTT can be reduced by superoxide radicals[13] and dye reduction is a measure of superoxide generation[14].

Free radicals have been implicated in surgical stress-induced damage[15] and lipid peroxidation, a marker of oxidative stress, has been shown to occur after surgery[16]. A definite time course of oxidative stress markers in arterial blood exists during open heart surgery[17]. Antioxidants can reverse liver metastasis induced by surgical stress[18] and damage after coronary bypass surgery[19]. There are a number of putative free radical generating sites in the cell that include the mitochondrial respiratory chain and the enzyme xanthine oxidase.

Xanthine oxidase has been implicated in surgical stress and increased plasma xanthine oxidase activity has been shown after limb surgery[20] and sepsis[21]. Xanthine oxidase inhibition also reduces haemorrhagic shock-induced bacterial translocation[22] and the present authors' earlier study demonstrated increased xanthine oxidase activity 60 min after surgical stress[6]. In the present study, it was found that the increase in xanthine oxidase activity seen after surgical stress was more prominent in the middle and crypt regions of the epithelium, compared with the villus. Xanthine

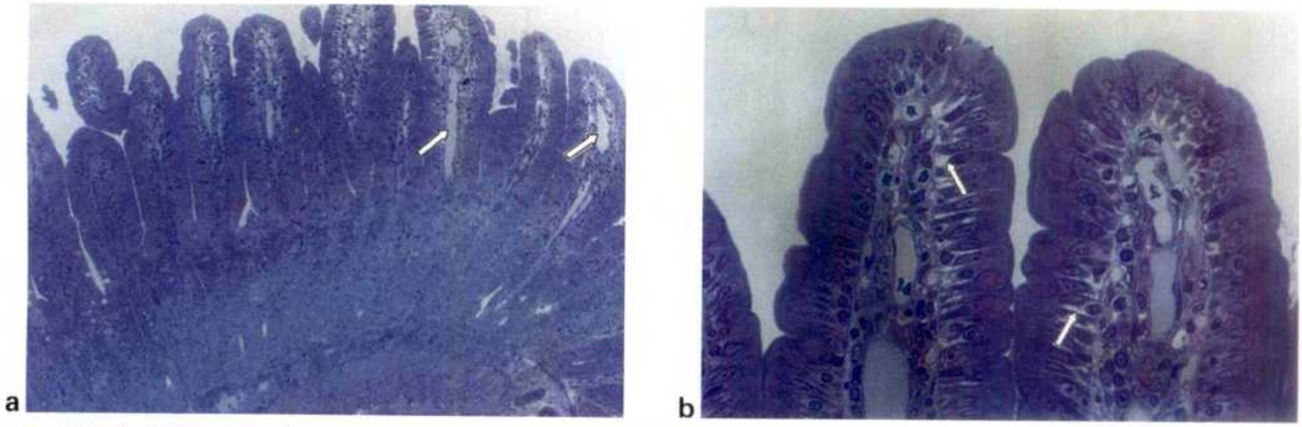

Fig. 5 Histological sections of small intestine from surgically stressed rats. Dilated blood vessels and widened intercellular spaces (arrows) are seen 60 min after surgical stress. **a** Original magnification × 90; **b** original magnification × 390 (toluidine blue stain)

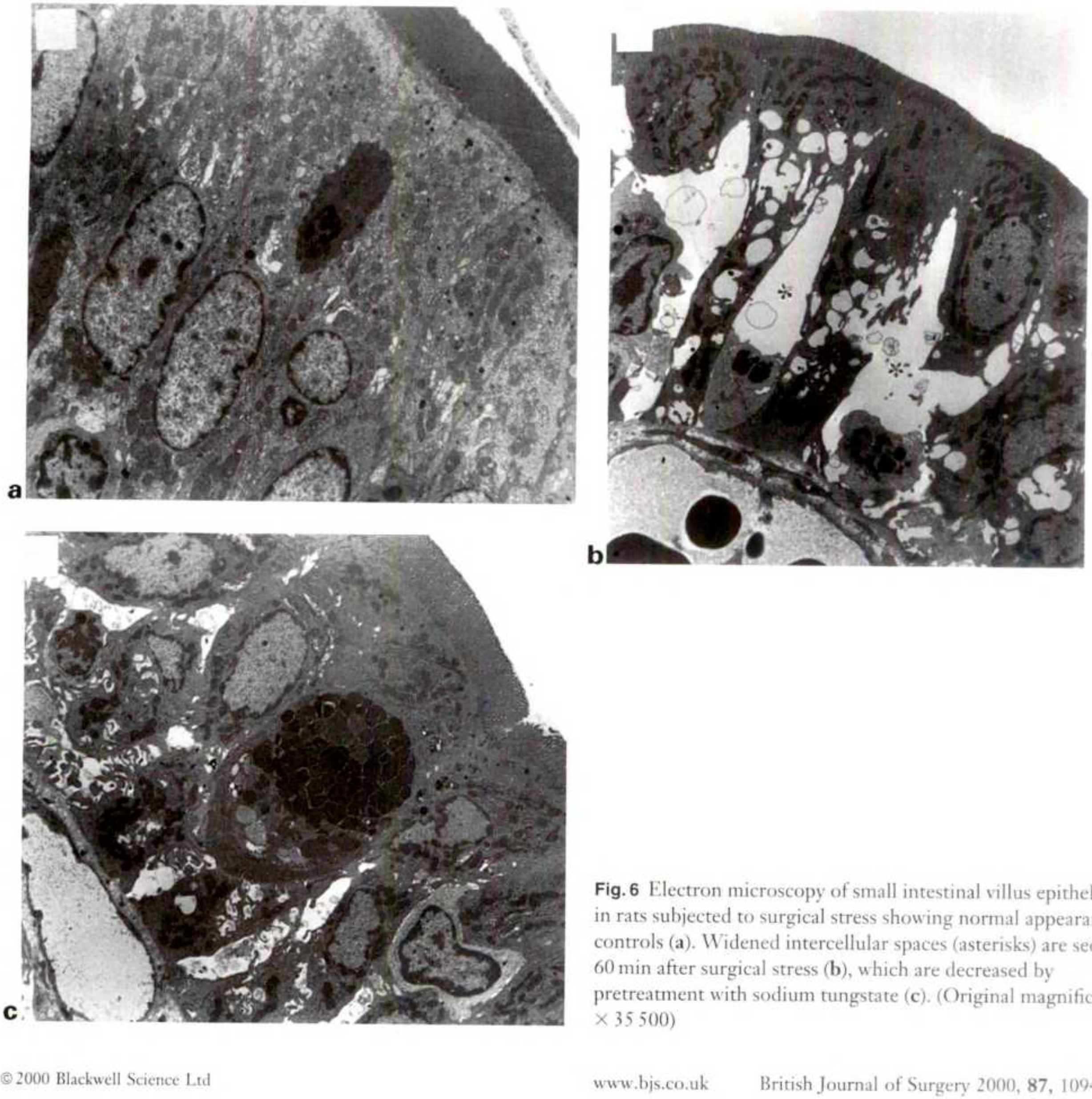

Fig. 6 Electron microscopy of small intestinal villus epithelium in rats subjected to surgical stress showing normal appearance in controls (**a**). Widened intercellular spaces (asterisks) are seen at 60 min after surgical stress (**b**), which are decreased by pretreatment with sodium tungstate (**c**). (Original magnification × 35 500)

oxidase is highly active in the enterocyte and is an important source of free radicals in the mucosa during ischaemia–reperfusion. Xanthine oxidase can also produce site-specific oxidant injury to organs remote from its site of release[23]. Xanthine oxidase activity can be inhibited completely by allopurinol[24], which protects against bacterial translocation and intestinal mucosal lipid peroxidation[25]. In the present study, xanthine oxidase activity could not be detected either in control rats or 60 min after surgical stress after pretreatment with allopurinol (data not shown). The increased MTT reduction after surgical stress was attenuated in allopurinol-treated rat intestine and this protection was more prominent in villus than crypt cells. Allopurinol is also an antioxidant, in addition to its inhibitory effect on xanthine oxidase[26] so experiments were repeated with another xanthine oxidase inhibitor, sodium tungstate, which depletes molybdenum, a cofactor for the enzyme[27]. Xanthine oxidase activity was similarly undetectable in enterocytes after treatment with tungstate (data not shown). In tungstate-treated rats inhibition of MTT reduction was similar, indicating that the increase in MTT reduction was to a certain extent caused by activation of xanthine oxidase, especially in cells of the villus region.

Another source of superoxide in the cell is the mitochondria, since approximately 1–2 per cent of the oxygen consumed by the mitochondria constitutively results in generation of superoxide[28]. Uncoupling of mitochondrial respiration may contribute to generation of free radicals, which are capable of altering mitochondrial function[29]. Mitochondrial function can be affected by surgical stress[30] and earlier observations from this laboratory indicated that there was mitochondrial dysfunction 60 min after surgical stress, with an increased MTT reduction in the presence of respiratory substrate and a decreased respiratory control ratio (R. Anup, P. Susama and K. A. Balasubramanian, unpublished observation). In the present study, pretreatment of animals with allopurinol or sodium tungstate protected mitochondria against the decrease in respiratory control ratio and concomitant increase in MTT reduction. Another characteristic feature of mitochondrial damage observed in the earlier study was initiation of the mitochondrial permeability transition. This damage can be effected by a number of inducers, including oxidants, and is the result of opening of a non-specific megapore in the inner mitochondrial membrane[31]. Inhibition of xanthine oxidase by allopurinol or sodium tungstate offered partial protection against this damaging phenomenon.

On histological examination, the intestine from surgically stressed rats showed vasodilatation and lamina propria oedema under light microscopy. Electron microscopy indicated increased intercellular spaces 60 min after stress, which suggested increased fluid movement between epithelial cells. This may also result in bacterial translocation seen in other studies[22]. Inhibition of intercellular widening, by pretreatment with allopurinol or sodium tungstate, implies that xanthine oxidase activation influences the widening of intercellular spaces and supports the hypothesis that xanthine oxidase mediates bacterial translocation[22].

In conclusion, these studies have shown that surgical stress produced by intestinal handling causes widespread damage to the intestinal epithelium, with both villus and crypt cells being affected. Increased generation of superoxide radicals in both villus and crypt cells was seen 60 min after stress, which was partly due to activation of xanthine oxidase. This activation was more prominent in the middle and crypt regions than the villus cells, and inhibition of xanthine oxidase activity by two separate inhibitors indicated an important role for this enzyme in superoxide generation. The xanthine oxidase inhibitors also protected against the damaging effects of intestinal handling on enterocyte mitochondria, including a decrease in the intercellular space widening seen in the intestinal epithelium. Xanthine oxidase may be an important mediator of surgical stress in the intestine.

Acknowledgements

Supported by the Wellcome Trust, London and the Council of Scientific and Industrial Research, Government of India. R.A. is a senior research fellow of the Council of Scientific and Industrial Research.

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Original article

Oesophageal resection for high-grade dysplasia in Barrett's oesophagus

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Background: The aims of this study were to evaluate the prevalence of invasive cancer in patients with high-grade dysplasia in Barrett's oesophagus and to verify whether a second endoscopy with multiple biopsies could improve the accuracy of preoperative diagnosis. In addition, the mortality, morbidity and survival rates in patients with high-grade dysplasia having oesophageal resection were recorded.

Methods: Fifteen patients were observed from 1982 to 1998; the first seven patients were offered primary oesophageal resection after diagnosis. The other eight patients underwent a second endoscopy with a median of 12 biopsies examined. All later underwent oesophageal resection.

Results: Invasive adenocarcinoma was found in five patients, with a minimal difference between the first and second periods (two of seven *versus* three of eight). There were no perioperative deaths. Early morbidity was observed in eight patients and late morbidity in four. The actuarial survival rate was 79 per cent at 5 years. The Karnofsky status was unchanged from preoperative values in 13 of 15 patients after a median follow-up of 46 months.

Conclusion: These patients with high-grade dysplasia had a 33 per cent probability of harbouring invasive oesophageal carcinoma but even a second endoscopy failed to identify patients with invasive tumour. Oesophagectomy was performed with no deaths and remains a rational treatment in patients fit for surgery.

Paper accepted 6 February 2000

British Journal of Surgery 2000, 87, 1102–1105

Introduction

Although endoscopic surveillance programmes for Barrett's oesophagus are currently recommended[1], the diagnosis of high-grade dysplasia in the endoscopic specimen is relatively rare[2]. When it does occur, it poses a clinical challenge for three reasons[3]: the diagnosis may be uncertain, the natural history of this lesion is not fully understood and there is no evidence in the medical literature to support any particular one of the variety of therapeutic strategies advocated. The options include strict endoscopic surveillance, treatment limited to the Barrett's mucosa (with endoscopic mucosectomy, laser ablation or photodynamic therapy) or a more aggressive therapy (removing the whole oesophagus). All of these options have their advantages and disadvantages, and the choice must be made after carefully balancing the risk to the patient and the availability of surgical or endoscopic expertise.

The aim of the present study was to determine the prevalence of associated cancer undetected by endoscopy and biopsy in patients with high-grade dysplasia in Barrett's oesophagus, and whether an endoscopic protocol with multiple biopsies could improve the accuracy of the endoscopic diagnosis. Finally, the mortality and early and late morbidity rates associated with oesophageal resection for high-grade dysplasia were recorded along with the long-term survival of these patients. The pathological findings in patients who had an oesophagectomy between 1982 and 1994 were compared with those who had surgery between 1995 and 1998, when a strict biopsy protocol for high-grade dysplasia in Barrett's oesophagus was routinely adopted.

Patients and methods

Patients with a diagnosis of high-grade dysplasia in Barrett's oesophagus between 1982 and 1994 were selected from a database containing all clinical, surgical and pathological data on patients referred to this centre with oesophageal carcinoma. Since 1995 patients with high-grade dysplasia in Barrett's oesophagus have been evaluated prospectively using a separate database. None of these patients had gross or microscopic evidence of invasive adenocarcinoma at the initial endoscopy and biopsy.

In the early part of the study, Barrett's oesophagus was defined as the presence of 3 cm or more of columnar epithelium above the gastro-oesophageal junction[4]; in recent years, Barrett's oesophagus has been defined as the presence of intestinal-type metaplastic epithelium in the oesophagus, regardless of its extent[5]. Dysplasia in Barrett's oesophagus was defined according to established criteria[6] and further classified as high-grade or low-grade/indefinite. Invasive carcinoma was defined as infiltration of carcinoma cells beyond the muscularis mucosa[7]; tumours were staged according to the tumour node metastasis system[8].

During the first part of the study, patients with high-grade dysplasia considered fit for surgery were offered oesophageal resection. Since 1995 the protocol proposed by Palley *et al.*[9] was adopted: the diagnosis of high-grade dysplasia was confirmed by a second pathologist and within a month a second endoscopy was performed with vital staining and biopsies every 2 cm of Barrett's mucosa, plus biopsies taken 1 cm distally, 1 cm proximally and 1 cm circumferentially from the site of the original dysplasia.

Patients who consented underwent subtotal oesophagogastrectomy using the Ivor–Lewis technique, with a stapled anastomosis between the oesophagus and the stomach performed above the arch of the azygos vein. If the Barrett's oesophagus extended up to the proximal part of the thoracic oesophagus, or if there were other reasons preventing the standard right thoracotomy approach, a transhiatal oesophagectomy was performed. When the Ivor–Lewis procedure was used, a standard lymphadenectomy with clearance of the periaortic, infracarinal and perioesophageal nodes was performed routinely. Postoperative deaths and complications were classified as early (within the first 30 days) or late.

Results

In the two intervals considered, some 581 patients with adenocarcinoma of the distal oesophagus or cardia (507 in the first period and 74 in the second) were treated. Patients with a preoperative diagnosis of high-grade dysplasia in Barrett's oesophagus represented only 3 per cent of the total (18 patients). Two of these refused surgery and one was ruled out because of respiratory insufficiency. The other 15 patients underwent oesophageal resection and formed the study group (seven patients in the first interval and eight in the second). They were all men with a median age of 69 (range 51–79) years. Seven of the 15 patients were on an endoscopic surveillance programme because of a known Barrett's oesophagus; the proportion of patients whose high-grade dysplasia was found during a surveillance programme slightly increased in the second interval (two of seven in 1982–1994 *versus* five of eight in 1995–1998). The strict biopsy protocol led to the identification of two patients with invasive carcinoma among those patients who had been referred to this unit with high-grade dysplasia and to the ruling out of high-grade dysplasia in one.

Typical gastro-oesophageal reflux symptoms (heartburn and acid regurgitation) were reported by 11 patients (four of seven in the first interval and seven of eight in the second); two patients also had chest pain and two had dysphagia. One patient complained of dyspeptic symptoms. Three patients were not symptomatic, however, and endoscopy was performed for various other reasons. One patient previously had antireflux surgery and one had undergone lobectomy for lung carcinoma. The duration of symptoms in the symptomatic patients was 9 (range 1–30) years with no difference between the two intervals. In the eight patients observed since 1995 (second interval) a median of 12 (range 5–9) biopsies were obtained at repeat endoscopy and a median of 0·23 (range 0·10–0·48) cm^2 of Barrett's mucosa was examined for each patient. A median of 4 (range 2–6) biopsies had been obtained from the three patients diagnosed at endoscopy in this unit in the first interval.

An Ivor–Lewis oesophagectomy was performed in 12 patients, while three had a transhiatal oesophagectomy (two because of a near-complete lining of the oesophagus with columnar epithelium and one because of a previous right thoracotomy for lower lobe lung cancer). There were no postoperative deaths. Early postoperative morbidity was observed in eight of 15 patients, and involved pleural effusion, pneumonia, urinary retention, diabetic decompensation, bleeding and chylothorax. The patient who bled and the one who developed a chylothorax needed reoperation. The mean postoperative hospital stay was 15 (range 11–21) days. Late morbidity was observed in four patients, the most common being anastomotic stricture, which was treated by endoscopic dilatation in three patients. One patient had delayed gastric emptying, treated with balloon dilatation of the pylorus.

The whole resected oesophagus was examined by the pathologist; a median of 14 (range 8–22) specimens were obtained from each resected oesophagus and five sections were examined from each embedded specimen. Invasive adenocarcinoma was found in five of 15 specimens. *Table 1* summarizes the histological findings and the gross appearance at endoscopy.

Follow-up was complete and ranged from 3 to 188 (median 46) months. Two patients died during follow-up, at 13 and 59 months, with no recurrent disease at the time of death (information obtained by telephone interview of relatives). The 5-year survival rate was 79 per cent; no

Table 1 Characteristics of Barrett's oesophagus and postoperative findings after oesophagectomy in patients with high-grade dysplasia

	No. of patients	Length of columnar epithelium (cm)*	Gross endoscopic appearance		No. with invasive tumour
			Normal	Nodularity, ulcer	
1982–1994 (no endoscopic protocol)	7	4 (3–15)	4	3	2
1995–1998 (endoscopic protocol)	8	6 (0·5–10)	5	3	3

*Values are median (range)

difference in survival was observed between patients with or without invasive tumour. The preoperative Karnofsky status was 90–100 in all patients. At a median of 46 (range 3–60) months after surgery the Karnofsky status was the same in all but two patients, whose Karnofsky score had worsened (to 60 and 50).

All three patients who did not have surgery were alive and well. One patient was on acid suppression therapy and a strict surveillance programme; high-grade dysplasia was not confirmed at the last two endoscopies. Two patients had intraluminal radiotherapy and antireflux treatment (one medical and one surgical). The follow-up for these three patients was 24, 15 and 13 months.

Discussion

There is circumstantial evidence that adenocarcinoma of the lower oesophagus and cardia is the outcome of the progression of dysplastic change in the intestinal-type epithelium that abnormally lines the distal part of the oesophagus[10]. However, the time it takes to progress from high-grade dysplasia to invasive adenocarcinoma is not known and remains one of the unsolved dilemmas in Barrett's oesophagus[11]. The finding of patients with high-grade dysplasia in Barrett's oesophagus is still uncommon, even at specialized centres. When it happens, this finding poses a serious clinical challenge. The first crucial point concerns the accuracy of the endoscopic diagnosis of high-grade dysplasia and whether any invasive adenocarcinoma can be ruled out before resection. Levine *et al.*[12] claimed that they were able to distinguish between high-grade dysplasia and invasive carcinoma with a 93 per cent accuracy rate using a careful endoscopic protocol. This was not the case in the present study; a third of the patients thought to have high-grade dysplasia had invasive adenocarcinoma and the use of a strict endoscopic biopsy protocol failed to improve the likelihood of distinguishing between dysplasia and carcinoma. Finding gross irregularity at endoscopy did not help in pinpointing the presence of invasive cancer. The data emerging from the present study are similar to those reported previously; the ability to differentiate between adenocarcinoma and high-grade dysplasia in eight small series ranged from 37 to 73 per cent[12–19]. There is no evidence at present that molecular biology markers (p53, p16, Ki67, DNA aneuploidy) or endoscopic ultrasonography can improve diagnostic accuracy[20].

The decision to operate for high-grade dysplasia should therefore be based on balancing the risk of overlooking an adenocarcinoma against the hazards of surgery. The overall mortality rate of oesophagectomy for high-grade dysplasia reported in the literature in the past 10 years has ranged from 14 per cent to zero; only two deaths have occurred in 130 patients (1·5 per cent)[12–19]. Such a low mortality rate for oesophagectomy probably applies only to patients with high-grade dysplasia and not to those having oesophagectomy for advanced tumours. Postoperative morbidity cannot be disregarded. Oesophagectomy carries a heavy burden of early and late complications. Two of the 15 patients described here needed reoperation owing to chylothorax and bleeding, and more than half the patients had some early complications. The late morbidity was represented almost exclusively by anastomotic strictures that were easily managed with endoscopic dilatation. Anastomotic strictures could be related to the routine use of a stapled anastomosis, especially when performed in an undilated oesophagus. This drawback is probably amply compensated, however, by the avoidance of anastomotic failure, a much more dangerous complication.

Although the quality of life was not measured, the Karnofsky score (an indicator of a patient's well-being) was collected prospectively in all patients. Most patients enjoyed a relatively normal life after surgery, except for two, who had a worsened Karnofsky index. Patients who had surgery had an 80 per cent chance of survival at 5 years and none died from recurrent disease. Their life expectancy appeared similar to that of normal 69-year-old men in Italy.

Adenocarcinoma of the oesophagus is a lethal disease; there is no effective therapy and surgery is only palliative if tumour cells have invaded the oesophageal wall and the adjacent lymph nodes. At the present time, the only way to cure oesophageal adenocarcinoma is to remove the tumour before it can become invasive. None of the present patients had positive lymph nodes and the tumour cells were still limited to the oesophageal mucosa in two of five patients, suggesting an excellent long-term prognosis. The alternative management would have been a very strict endoscopic follow-up or mucosal ablation with the laser or phototherapy. It is not yet clear whether surveillance can detect progression of the disease before it spreads. As regards mucosal ablation, photodynamic therapy is currently the most promising treatment[21].

Less invasive, alternative therapies for high-grade dysplasia in Barrett's oesophagus are needed urgently. In the absence of randomized clinical trials comparing resection with surveillance, surgical resection of the oesophagus is a rational treatment that should be offered to suitable patients, providing that it is performed in specialized centres with expertise in oesophageal surgery.

Acknowledgements

This work was supported in part by the grant N. 731/02/96 of the Veneto Region.

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Original article

Preoperative risk analysis in patients with adenocarcinoma or squamous cell carcinoma of the oesophagus

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Background: The outcome after oesophagectomy depends not only on the surgical procedure itself but can be improved by the selection of patients based on a preoperative risk score.

Methods: In order to compare the preoperative risk for different histological subtypes of oesophageal carcinoma, 221 patients with a squamous cell carcinoma (SCC) and 104 patients with an adenocarcinoma (AC) were enrolled in a prospective study. The preoperative assessment included socioeconomic status, alcohol and tobacco consumption, general and nutritional status, and pulmonary, cardiovascular, hepatic and renal function.

Results: More patients with an SCC were 'blue collar' and with an AC were 'white collar' workers ($P < 0.001$). Alcohol and tobacco consumption was higher in patients with an SCC ($P < 0.01$ and $P < 0.05$ respectively). The preoperative forced expiratory volume, arterial partial pressure of oxygen and the aminopyrine breath test showed more severely compromised pulmonary and hepatic function in patients with an SCC ($P < 0.05$ for all variables). Some 50 per cent of patients with an AC were overweight with a higher body mass index ($P < 0.001$). More patients with an AC had severely impaired cardiac function ($P < 0.01$).

Conclusion: Patients with SCC and AC of the oesophagus differed regarding their socioeconomic and preoperative risk factors for surgery.

Paper accepted 5 February 2000

British Journal of Surgery 2000, 87, 1106–1110

Introduction

In a recent study it was demonstrated that the preoperative risk in patients with oesophageal cancer can objectively be assessed using a composite risk score of individual organ dysfunction[1]. In addition, selection of patients based on this risk score improved the postoperative mortality rate associated with oesophagectomy[1].

The aim of this study was to analyse differences in demographic data, aetiological factors and preoperative organ dysfunction between patients with squamous cell carcinoma (SCC) and adenocarcinoma (AC) of the oesophagus.

Patients and methods

During a 6-year interval (1 January 1989 to 31 December 1994) 599 patients with an oesophageal cancer were seen at the Department of Surgery, Technische Universität München. All patients had detailed preoperative oncological staging of the tumour. Some 274 had palliative treatment (25 resection and 249 radiotherapy and/or chemotherapy) for an advanced tumour and/or poor physical status. Sixty-five of these patients had the histologically proven diagnosis of an AC and 209 had an SCC. A further 325 patients (54·3 per cent) with an oesophageal cancer had curative treatment (221 SSC (51·4 per cent of all SCCs) and 104 AC (61·6 per cent of all ACs)) and were included in this prospective investigation. Seventy-three patients (33·0 per cent) with a locally advanced SCC received neoadjuvant radiochemotherapy according to a standard protocol[2]; 21 patients (20·2 per cent) with an AC received chemotherapy only. The mode and extent of oesophageal resection depended on the location and histology of the tumour as described elsewhere[3,4]. The postoperative tumour node metastasis (TNM) stage of the resected specimen was according to the Union Internacional Contra la Cancrum (*Table 1*)[5]. Both 30- and 90-day postoperative mortality rates were calculated.

Table 1 Pathological and epidemiologic data of 221 patients with squamous cell carcinoma and 104 patients with adenocarcinoma of the oesophagus

	Squamous cell carcinoma (n=221)	Adenocarcinoma (n=104)	P
Median (range) age (years)	53 (35–79)	61 (19–82)	< 0·001
Sex ratio (M : F)	193 : 28	98 : 6	n.s.
Profession			
White collar	106 (48·0)	83 (79·8)	< 0·001
Blue collar	115 (52·0)	21 (20·2)	
Tumour stage*			
pT_1	46 (20·8)	28 (26·9)	< 0·01
pT_2	47 (21·3)	39 (37·5)	
pT_3	109 (49·3)	33 (31·7)	
pT_4	19 (8·6)	4 (3·8)	
Node stage*			
pN_0	97 (43·9)	43 (41·3)	n.s.
pN_1	124 (56·1)	61 (58·7)	
Metastasis stage*			
pM_0	201 (91·0)	85 (81·7)	n.s.
pM_1	20 (9·0)	19 (18·3)	

Values in parentheses are percentages unless otherwise indicated. *Pathological tumour node metastasis stage. n.s., Not significant

All patients had preoperative assessment including documentation of all relevant demographic data, socioeconomic status as well as aetiological factors such as alcohol and tobacco consumption. In addition a preoperative risk analysis was performed by evaluating general status, nutritional status with body-weight and weight loss, and cardiovascular, pulmonary, hepatic and renal function (*Table 2*).

As a measure of the socioeconomic status, the patient's profession was assigned to one of the classes more closely described as 'white collar' or 'blue collar'. The occupations classified by 'collar' are described elsewhere[6].

Alcohol consumption was determined by a patient questionnaire recording type and quantity of alcoholic beverages. On the basis of the reported alcohol intake, the average daily quantity of alcohol consumed was computed in grams per day (*Table 2*). Nicotine consumption was calculated in terms of the number of cigarettes smoked per day.

To assess the patient's preoperative condition the body mass index (BMI = weight/size^2) was used[7]. Normal weight was defined according to the average weight of the German population[8]: for women a BMI of 19–22 kg/m^2 and for men 21–25 kg/m^2. In addition, weight loss over the previous 6 months was recorded as a percentage of the normal body-weight.

Table 2 Variables used for evaluation of the preoperative risk for 221 patients with squamous cell carcinoma and 104 patients with adenocarcinoma of the oesophagus

- Age
- Sex
- Socioeconomic status (white collar, blue collar)
- Tobacco consumption (cigarettes per day)
- Alcohol consumption (<75, 75–150, >150 g/day)
- General status
  - Karnofsky index (0–100)
  - Body mass index (women 19–22 kg/m^2, men 21–25 kg/m^2)
  - Weight loss (percentage of body-weight)
- Cardiovascular function
  - Electrocardiogram (normal or abnormal)
  - Chest radiograph (normal or abnormal)
  - Cardiologist's evaluation (normal risk, increased risk, high risk)
- Pulmonary function
  - Pa_{O_2} (mmHg)
  - Pa_{CO_2} (mmHg)
  - Vital capacity (percentage of normal)
  - FEV_1 (percentage of normal)
- Hepatic function
  - Child's classification (A–C)
  - Aminopyrine breath test
- Renal function
  - Urea (mg/dl)
  - Creatinine (mg/dl)
  - Creatinine clearance (ml/min)

Pa_{O_2}, arterial partial pressure of oxygen; Pa_{CO_2}, arterial partial pressure of carbon dioxide; FEV_1, forced expiratory volume

Table 3 Classification of individual organ dysfunction in 221 patients with squamous cell carcinoma and 104 patients with adenocarcinoma of the oesophagus

Cardiovascular function	
Normal	Normal risk for major surgical procedure
Compromised	Increased risk for major surgical procedure
Severely impaired	High risk for major surgical procedure
Pulmonary function	
Normal	Vital capacity > 90%, FEV_1 > 90%, Pa_{O_2} > 70 mmHg
Compromised	Two of three parameters decreased
Severely impaired	All three parameters decreased
Hepatic function	
Normal	Child's A, aminopyrine breath test > 0·4
Compromised	Child's A or B, aminopyrine breath test < 0·4
Severely impaired	Child's C, cirrhosis
Renal function	
Normal	Creatinine clearance > 70 ml/min
Compromised	Creatinine clearance < 70 ml/min

FEV_1, forced expiratory volume; Pa_{O_2}, arterial partial pressure of oxygen

The preoperative risk analysis of individual organ systems was based on the patient's history and objective measurement of single variables. The variables relating to the different organ systems are listed in *Table 2*. The criteria for the classification of 'normal', 'compromised' and 'severely impaired' organ dysfunction are shown in *Table 3*. The value of this classification for individual organ dysfunction is based on a multivariate analysis of the postoperative outcome, described previously[1].

To assess cardiovascular risk, all patients had an electrocardiogram and chest radiograph, and were seen by a cardiologist who initiated further detailed investigation when indicated. Depending on these results, the cardiologist classified the preoperative risk as 'normal', 'compromised' or 'severely impaired'.

Statistical evaluation was done by descriptive statistics: mean(s.e.m.) and median with lower and upper quartiles. The test statistics were performed with either the *t* test, the Wilcoxon test or the χ^2 test (Fisher's exact test or χ^2 test including Yates' correction). $P < 0{\cdot}05$ was considered to be significant. All evaluations were performed using the statistical package SPSS for MS-WINDOWS, release 7·5 (SPSS, Chicago, Illinois, USA).

Results

Demographic and pathological data

The epidemiological data comparing 221 patients with an SCC and 104 with an AC are displayed in *Table 1*. At the time of diagnosis, the median age of patients with an AC was 8 years greater than that of patients with an SCC ($P < 0{\cdot}001$). The male to female ratio was not significantly different between the two histological subtypes. Patients with an AC were diagnosed at an earlier T stage than those with an SCC. This is demonstrated by a significantly higher proportion of tumours that had not infiltrated the adventitia (T_1 and T_2 tumours). There were no differences regarding the N and M stage between the different histological subtypes. The 30- and 90-day mortality rate was significantly higher in patients with an SCC (14·0 and 18·1 per cent respectively) than in patients with an AC (3·9 and 8·7 per cent). This difference remained significant even if the analysis was restricted to patients with an SCC who did not have neoadjuvant radiochemotherapy (9·5 and 13·5 per cent respectively).

Socioeconomic status (*Table 1*)

Comparing the socioeconomic status of the two groups, a significantly higher proportion of patients with an AC were classified as 'white collar' whereas a higher proportion of patients with an SCC were 'blue collar'.

Alcohol and tobacco consumption (*Table 4*)

In both groups the average alcohol and tobacco consumption was abnormally high but it was significantly greater in patients with an SCC ($P < 0{\cdot}01$). The percentage of patients with a high alcohol consumption was also greater in the SCC group ($P < 0{\cdot}001$).

Table 4 Differences in nutritional status, and alcohol and tobacco consumption for 221 patients with squamous cell carcinoma and 104 patients with adenocarcinoma of the oesophagus

	Squamous cell carcinoma (*n*=221)	Adeno-carcinoma (*n*=104)	*P*
Alcohol			
Level of consumption*			<0·001
Normal	67 (30·3)	60 (57·7)	
Medium	111 (50·2)	40 (38·5)	
High	43 (19·5)	4 (3·8)	
Quantity (g per day)†	76 (60–126)	54 (30–80)	<0·01
Nicotine			
Quantity (cigarettes per day)†	30 (20–50)	20 (20–30)	<0·05
Non-smoker*	70 (31·7)	50 (48·1)	<0·005
Nutritional status			
Weight (kg)‡	70(2)	77(2)	<0·0003
Body mass index†	23 (21–25)	25 (23–26)	<0·001
Overweight/underweight*			<0·0001
Underweight	28 (24·1)	1 (1·9)	
Normal weight	121 (45·9)	45 (48·1)	
Overweight	72 (30·0)	58 (50·0)	
Weight loss (%)†§	7 (3–14)	6 (4–14)	n.s.

*Values in parentheses are percentages; †values are median (interquartile range); ‡values are mean(s.e.m.). §In the previous 6 months. n.s., Not significant

Some 31·7 per cent of patients with an SCC and 48·1 per cent with an AC were non-smokers ($P < 0{\cdot}005$). The median number of cigarettes smoked per day was significantly greater in patients with an SCC ($P < 0{\cdot}05$).

General and nutritional status (*Table 4*)

The difference in nutritional status between patients with an SCC and an AC was particularly marked. Before surgery patients with an SCC weighed a mean of 70 kg compared with 77 kg for those with an AC ($P < 0{\cdot}0003$). The difference was also evident using the BMI ($P < 0{\cdot}001$). Some 24·1 per cent of patients with an SCC were underweight compared with only 1·9 per cent of patients with an AC. On the other hand, 50·0 per cent of the patients with an AC were overweight compared with only 30·0 per cent of those with an SCC ($P < 0{\cdot}0001$). Weight loss over the 6 months before diagnosis was not significantly different between the two groups.

Preoperative risk assessment (*Table 5*)

Although the overall pulmonary risk was not significantly different between the two groups, the variables forced expiratory volume (FEV_1) and arterial partial pressure of

Table 5 Differences in organ dysfunction for 221 patients with squamous cell carcinoma and 104 patients with adenocarcinoma of the oesophagus

	Squamous cell carcinoma (*n*=221)	Adenocarcinoma (*n*=104)	*P*
Pulmonary risk*			n.s.
Normal 1	144 (65·1)	78 (75·0)	
Medium 2	66 (29·9)	22 (21·2)	
Poor 3	11 (5·0)	4 (3·8)	
FEV_1†	82·5(2·3)	93·7(4·3)	< 0·05
Vital capacity†	88·2(1·7)	91·2(2·4)	n.s.
PaO_2 (mmHg)†	72·7(1·1)	77·5(1·6)	< 0·05
$PaCO_2$ (mmHg)†	37·2(0·7)	35·2(0·8)	n.s.
Cardiovascular risk*			< 0·01
Normal	178 (80·5)	73 (65·2)	
Compromised	38 (17·2)	31 (27·7)	
Severely impaired	5 (2·3)	8 (7·1)	
Hepatic function*			< 0·05
Normal	143 (64·7)	78 (75·0)	
Compromised	54 (24·4)	23 (22·1)	
Severely impaired	24 (10·9)	3 (2·9)	
Aminopyrine breath test†	0·38(0·02)	0·52(0·03)	< 0·05
Renal function*			< 0·001
Normal	212 (95·9)	86 (82·7)	
Compromised	9 (4·1)	18 (17·3)	

*Values in parentheses are percentages; †values are mean(s.e.m.). FEV_1, forced expiratory volume; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; n.s., not significant

oxygen (PaO_2) were significantly decreased ($P<0{\cdot}05$ for both) in patients with an SCC. The evaluation of cardiovascular function by a cardiologist and the assessment of renal function demonstrated an overall increased risk for patients with an AC ($P<0{\cdot}01$ and $P<0{\cdot}001$ respectively). Impaired hepatic function was significantly more common in patients with an SCC ($P<0{\cdot}05$), also demonstrated by a significantly decreased aminopyrine breath test ($P<0{\cdot}05$).

Discussion

Morbidity and mortality rates after oesophagectomy are not only influenced by the surgical procedure itself but also the preoperative physiological status of the patient[9,10]. The preoperative risk of death after oesophagectomy can objectively be assessed using a composite risk score that aids patient selection for oesophagectomy. Using this composite risk score the 30-day mortality rate decreased from 9·4 to 1·6 per cent in a prospective investigation[1].

In an earlier analysis it was demonstrated that patients with an AC have a better prognosis than those with an SCC, especially patients with an early tumour stage[11,12]. Law *et al.* demonstrated a difference in the postoperative mortality rate between patients with SCC and AC that was related to the postoperative course and the rate of postoperative complications[9,12]. Assuming that this variation in mortality rate is based on the preoperative risk, the aim of this study was to compare preoperative organ dysfunction in patients with these two histological subtypes of oesophageal cancer, including demographic data and aetiological factors.

Smoking is an aetiological factor for both histological subtypes of oesophageal carcinoma. Smokers are three to four times more likely to develop an SCC and two to three times more likely to develop an AC[13,14]. In accordance with the literature, in the present investigation only 31·7 per cent of patients with an SCC were non-smokers compared with 48·1 per cent of those with an AC[14,15]. These differences probably explain the poor pulmonary function observed in patients with an SCC.

Pulmonary dysfunction constitutes the most frequent postoperative complication seen after oesophagectomy[1,9,16]. This concords with the high rate of preoperative pulmonary disorders, 34·9 per cent in patients with an SCC and 25·0 per cent in patients with an AC. FEV_1 and PaO_2 were significantly lower in patients with an SCC. Law *et al.*[9] reported that an average FEV_1 of 94 per cent was associated with a favourable postoperative course after oesophagectomy, compared with 81 per cent in patients with complications.

Another important factor influencing the postoperative course is preoperative liver function[1]. High alcohol consumption is known as an aetiological factor for SCC and a cofactor for AC[15,17,18]. In the present study patients with an SCC were significantly more likely to have poor hepatic function as demonstrated by a lower aminopyrine breath test. This is a more sensitive detector of liver dysfunction than the Child's classification and predicts the presence of cirrhosis[19,20]. A possible explanation for the poor liver function is alcohol consumption; both the percentage of heavy drinkers and the average amount of alcohol consumed per day were significantly higher in the SCC group. These results are consistent with other reports, although in all studies the reported alcohol intake was based on the history and therefore influenced by the patient's reliability[17,21].

Regarding the nutritional status, in both groups about half of the patients were of normal weight. In the AC group the remaining patients were overweight, whereas only 30·0 per cent of patients with an SCC were overweight and 24·1 per cent in this group were classified as underweight. A possible explanation for this proportion of underweight patients is that patients with an SCC generally present with an advanced tumour which usually correlates with progressive cachexia. Another reason for the different weight distribution and BMI relates to the dietary habit, particularly increased caloric intake[19].

Patients with an SCC have a greater alcohol and nicotine consumption than patients with an AC. This results in considerably impaired pulmonary and hepatic function. Patients with an AC have an increased cardiovascular risk compared with patients with an SCC. The differences in preoperative risk should be taken into consideration when planning oesophagectomy in patients with SCC and AC. Knowledge of specific preoperative risk factors might help to minimize postoperative morbidity.

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Original article

Multicentre study of thyroid nodules in patients with Graves' disease

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Background: The association of Graves' disease with thyroid nodules and thyroid carcinoma is rarely reported. The incidence seems to be increasing according to recent literature. The aim of this multicentre study was to review patients who had surgery for Graves' disease associated with thyroid nodules, and to evaluate the risk of thyroid carcinoma.
Methods: A retrospective study was made of 557 consecutive patients who underwent operation for Graves' disease between 1991 and 1997 in five endocrine surgery departments. Each patient underwent clinical, biochemical, ultrasonographic and scintigraphic evaluation. None of the patients had had previous radioactive iodine therapy or external irradiation. Surgery consisted of either a subtotal or total thyroidectomy.
Results: Nodules were observed before operation in 140 patients (25·1 per cent). Thyroid carcinoma was diagnosed in 21 patients (15·0 per cent), always inside a nodule. The incidence of thyroid carcinoma associated with Graves' disease was 3·8 per cent (21 of 557 patients): 20 papillary and one follicular carcinoma. The carcinoma was multifocal in two patients. Tumour diameter ranged from 2 to 25 mm. A nodule was palpable in four patients.
Conclusion: This multicentre study of patients having thyroidectomy for Graves' disease showed that 3·8 per cent had a carcinoma; the rate of carcinoma in cold nodules was 15·0 per cent. Surgery should be advised in any patient with Graves' disease and a thyroid nodule; the operation should be total thyroidectomy.

Presented to the annual meeting of British Association of Endocrine Surgeons, Edinburgh, UK, 28 May 1999
Paper accepted 2 March 2000
British Journal of Surgery 2000, 87, 1111–1113

Introduction

Thyroid nodules are common in patients with Graves' disease; they raise concern about coexisting thyroid malignancy. The authors have previously reported that patients with Graves' disease and a thyroid nodule have a very high risk of thyroid cancer[1]. Thyroid carcinomas associated with Graves' hyperthyroidism are more aggressive than those arising in patients with non-autoimmune hyperthyroidism or in euthyroid patients[2,3]. The pathogenic relationship between thyroid carcinoma and Graves' disease is still obscure. The preoperative investigations for thyroid nodules and thyroid carcinoma in patients with Graves' disease have not yet been established.

The Editors have satisfied themselves that all authors have contributed significantly to this publication.

The aim of this study was to determine the incidence of thyroid nodules or carcinoma in a large population of patients with Graves' disease, including the clinical features, methods of diagnosis and place of operation.

Patients and methods

A total of 557 consecutive patients who had thyroidectomy for Graves' disease between 1991 and 1997 in five endocrine surgery units in western France were studied retrospectively. Every patient underwent clinical, biochemical, ultrasonographic and scintigraphic evaluation. Patients with toxic nodular goitre were excluded, accepting the difficulty in scintigraphic evaluation of nodules less than 1 cm in diameter. No patient had a history of previous neck irradiation or radioactive iodine therapy. All patients had undergone surgery because of recurrence of hyperthyroidism after 18 months of medical treatment or because a thyroid nodule was detected. Surgical treatment consisted of near-total or total thyroidectomy. Patients with thyroid carcinoma underwent total thyroidectomy. Paratracheal and laterocervical lymph nodes were resected when macroscopically involved. Frozen-section and histopathological examination were performed systematically.

Results

A thyroid nodule was detected before operation in 140 patients (25·1 per cent of the study population). The nodule was palpable in only 40 patients (four carcinomas), whereas ultrasonography was positive in 116 cases. Scintigraphy showed areas of diminished uptake (cold nodules) in only 54 patients. Thyroid carcinoma was diagnosed histologically in 21 patients, always inside a nodule. The overall incidence of thyroid carcinoma associated with Graves' disease was 3·8 per cent, rising to 15·0 per cent if only patients with Graves' disease and a thyroid nodule were considered. All thyroid carcinomas were diagnosed by frozen-section examination and total thyroidectomy was performed in each case. Lymph nodes were involved in only one patient. The age of the patients (six men and 15 women) at operation ranged from 11 to 80 (mean 40) years. Pathological findings consisted of 20 papillary carcinomas and one follicular carcinoma; two were multifocal. The diameter of the tumours ranged from 2 to 25 mm.

Only four of the carcinomas were palpable, representing 10 per cent (four of 40) of all palpable nodules. The remaining 17 carcinomas were all impalpable (i.e. 17 per cent of the 100 impalpable nodules detected by preoperative imaging).

Discussion

The incidence of thyroid nodules in patients with Graves' disease is reported as 20–25 per cent in the literature[1,4]. The incidence of thyroid carcinoma is more frequently reported. The present study showed that 3·8 per cent of 557 patients with Graves' disease had thyroid cancer. All occurred within a nodule and thyroid cancer occurred in 15·0 per cent of patients with associated nodules. The incidence ranges from 2·6 to 9·3 per cent in recent studies, and may be increasing[1,4–7].

Explanations for the increasing incidence could include better nodule detection, differences in the extent of thyroid resection and the number of histological sections examined per specimen. Irradiation of the neck is another important factor that may increase the incidence[5,8–10], but no patient had this in the present study. Because of the high incidence of carcinoma in a thyroid nodule, the authors and others[1,2,5,6] recommend surgery when nodules are detected during evaluation for Graves' disease.

The methods of preoperative diagnosis of thyroid nodules associated with Graves' disease are not well established. The nodules are often small and difficult to palpate within a Graves' goitre. The best way to detect such nodules is probably by ultrasonography, which detected thyroid nodules in 116 of 140 patients in the present series. Thyroid scintigraphy documented only 54 cold nodules. Ultrasonography could also guide fine-needle aspiration biopsy (FNAB) of impalpable nodules. However, FNAB is difficult for small nodules, and risks haemorrhage in a Graves' goitre. Furthermore, the hyperplastic tissue of Graves' disease may increase the cytological diagnosis of follicular neoplasm[8]. Japanese authors advise radiographic imaging of the neck with soft X-rays to search for foci of calcification, which are highly suspicious of malignancy[11].

The clinical course of patients with a carcinoma associated with Graves' disease was not unusual in this study. This contrasts with other reports[2,6] where aggressive cancers were found, the suggestion being that thyroid-stimulating immunoglobulins may provide continued thyroid stimulation even in the presence of suppressed thyroid-stimulating hormone levels[12]. Suppressive therapy must be administered systematically.

In conclusion this report confirms that one-quarter of patients with Graves' disease have associated thyroid nodules. The authors suggest that patients with Graves' disease should be screened for thyroid nodules by ultrasonography. As, in the present study, 15·0 per cent of these nodules were malignant, the authors recommend thyroidectomy for patients with Graves' disease and a thyroid nodule. Total thyroidectomy should be considered because previous reports have documented the aggressive nature of carcinomas in this condition.

Acknowledgement

The authors thank Dr B. Harrison, Northern General Hospital, Sheffield for help in reviewing the work.

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Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double spacing

Venous ulcer healing by four-layer compression bandaging is not influenced by the pattern of venous incompetence

Sir

We read this paper with interest (*Br J Surg* 1999; **86:** 1437–40). Our own recent findings are similar to those of Guest *et al*[1]. We agree that the overall pattern of venous reflux has no influence on ulcer healing rates but, in keeping with findings from Edinburgh[2], we noted that patients with ulcerated limbs and reflux in the popliteal vein were at risk of delayed healing.

We wonder whether the authors could comment on the following points:

1. The authors concluded that previous deep vein thrombosis was a risk factor for delayed healing when there was no statistically significant difference[2].
2. How can the power of an analysis be increased by further dividing patients into two groups after the conclusion of a study?
3. We have been unable to show any benefit from surgery over and above compression bandaging in terms of ulcer healing[3]. The authors state that there is some evidence that superficial venous surgery may improve ulcer healing but the papers cited[4,5] fail to provide such evidence
4. Chronic venous leg ulcers were defined as being present for at least one month and the authors found a lower ulcer healing rate than in their original series from Charing Cross[6]. The earlier study however, described a cohort in which over one third of ulcers had been present for less than 4 weeks which, we believe, explains the difference in healing rates between the two studies.

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Authors' reply

Sir

We thank Barwell *et al.* for their interest in our work and are pleased to respond to the points raised in their letter:

1. While this study only showed a *trend* that patients with a previous deep vein thrombosis healed worse, the numbers were small, raising the possibility of a type II error. When combining this trend with the findings of referenced trials which found *significantly* worse healing in this group, we thought this a reasonable conclusion to draw.
2. It was always the intention to examine the healing of those patients with deep vein reflux. Therefore the healing rate of all patients with deep vein incompetence was compared with those patients with no deep vein incompetence. This part of the analysis was not simply added on 'after the conclusion of the study'.
3. The study did not look at the issue of the benefit of surgery in any depth. That superficial surgery may improve ulcer healing reflects opinion of published work which generally shows better healing rates in patients undergoing simple venous surgery compared with patients having compression therapy alone. This may represent patient selection as none of these studies was a randomized controlled trial. We have also been unable to demonstrate any significant benefit when performing additional simple venous surgery and therefore we support the sentiments of Barwell *et al.* on this point.
4. This difference in the two studies is well noted and may have contributed in some way to the poorer healing rate in the second study.

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Comparison of cognitive function and quality of life after endovascular or conventional aortic aneurysm repair

Sir

This article (*Br J Surg* 2000; **87:** 443-7) is a timely reminder that the quality of life of patients following endolumenal repair must not be assumed to improve just because the procedure is associated with less time in the ITU and Hospital compared with open surgery. However, the authors did explain that the two groups of patients (open and endolumenal) were not matched. The endolumenal group were reported as high risk with many not suitable for open repair. Further, the type of endolumenal repair undertaken in 30 of the 34 patients in this group, involved more open surgery than other PTFE methods 1 including dissection of one common iliac artery and the construction of 4 separate anastomoses involving prosthesis and artery. This surgery is more invasive than the bilateral, or in some cases unilateral, groin incisions for femoral artery exposure required for deployment of most of the modern devices. It is possible that the more extensive surgical intervention employed by the authors has had a more significant effect on the quality of life assessment in this group.

For these reasons, the results of this study should not be exrtrapolated to the majority of endovascular repairs which are currently carried out. There will be general agreement with the authors that the present EVAR I and II randomized trials will better answer questions regarding quality of life after endovascular repair.

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1 Jenkins M, Adiseshiah M. Aortomonoiliac endografting. It does not have to be that difficult. *J Endovasc Surg* 1997; 4: 425–6.

Authors' reply

Sir

We thank Mr Adiseshiah for his interest in our article. Our study was conducted between the years 1996–98 and reflects the nature of endovascular aneurysm repair in Leicester at that time. It is true that most of the patients in the endovascular group were treated with an aortouni-iliac device. We conclude from our study that the decision to offer endovascular therapy should not be made on the expectation of improved quality of life. There is no evidence to believe that this conclusion would be any different for bifurcated devices. We agree with Mr Adiseshiah that the present EVAR trials will provide further data to address this issue.

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Diagnostic accuracy of needle-localized open breast biopsy for impalpable breast disease

Sir

Verkooijen *et al.* (*Br J Surg* 2000; **87:** 344–7) fail to distinguish between the accuracy of needle localization open breast biopsy (NLBB) in excising a designated lesion and interpretation of abnormal radiological features on inital mammography. Retrospective analysis will raise the level of suspicion for any lesion not previously biopsied but deemed malignant on latest imaging. However, failure to recognize a lesion in retrospect is not synonymous with omitting to excise a mammographic abnormality of uncertain identity but which has nevertheless been accurately localized. This occurs in 1–2 per cent of NLBB procedures[1,2].

In the 4 patients with a false negative result, did the specimen radiograph contain a discrete abnormality resembling the localized lesion? Compression and magnification views can be employed and additional tissue removed when indicated. Failure to excise a lesion intended for localization represents a true false negative result and reflects adversely on the technique of NLBB. Corroborative specimen radiography and accurate placement of the wire to within 1–2 cm of the lesion are essential components of successful NLBB. The surgeon must be familiar with mammographic interpretation, have a clear understanding of the spatial relationship between guide-wire and lesion and place the skin incision in proximity to the site of excision. We have described a method of localization whereby the wire is inserted by the surgeon and pursues the shortest course within the breast[3]. In studies of 950 patients using this technique all lesions have been correctly localized and removed at first surgery with clear margins and optimum cosmesis.

The length of follow up to verify true negativity is arbitrary, but claims of significant attrition of sensitivity and negative predictive value with longer follow up are not substantiated.

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1 Thompson WR, Bowen JR, Dorman BA *et al.* Mammographic localisation and biopsy of non-palpable lesions. *Arch Surg* 1991; **126:** 730.
2 An audit of screen-detected breast cancers for year of screening April 1997 to March 1998 *NHS Breast Screening Programme and British Association of Surgical Oncology* April 1999.
3 Querci della Rovere G. Benson J.R., Morgan M., Warren R. & Patel A. Localisation of impalpable lesions — a surgical approach. *Eur J Surg Oncol* 1996; **22:** 478–82.

Authors' reply

Sir

We fully agree with Benson and Querci della Rovere's definition of a 'truly false negative result', i.e. failure to excise a lesion intended for localization. According to this definition, all failures in our series qualified as such. On the other hand, we disagree with the authors on their supposition that placement of the localization wire within a 1–2 cm distance of the lesion may be recognized as 'accurate'. It is our firm belief that this interpretation is too flexible for optimal quality. Furthermore, the authors advocate wire insertion by the surgeon. We confirm the importance of precise needle positioning, regardless of which specialist performs the localization procedure, as long as he or she is optimally qualified.

The main message of our article is two-fold. First, the emphasis that should be placed on close collaboration between surgeons, pathologists and radiologists in optimizing and interpreting the results of NLBB. Only with a multidisciplinary approach can the number of missed breast cancers be kept to a minimum. Second, we are convinced that our series reflects the significance of long-term follow-up for the evaluation of the diagnostic performance of NLBB, as three of the six missed carcinomas were detected after a follow-up period of more than 3 years.

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Electronic evaluation of the value of double gloving

Sir

We read with interest the paper by Caillot *et al.* (*Br J Surg* 1999, **86**:1387–90) and were surprised that of 15 laparoscopic procedures there were 29 exposures. In our practice it is very rare for laparoscopic surgeons to be doubled gloved except during high risk cases. Could the authors please elaborate on the number of wet gowns during laparoscopic surgery? Was there any correlation between the experience of the surgeon and the number of exposures?

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Authors' reply

We thank Drs K. and N. Bhattacharya for their interest in our article. We have defined exposure as involvement of an individual surgical team member. The 29 exposures in 15 laparoscopic procedures simply indicate there were usually 2 operators at risk for an incident during each intervention.

During these 29 laparoscopic exposures, no glove porosity was electronically detected and the 7 alarms recorded were due to single gloving rupture ($n = 4$) and to gown wetting, essentially at the cuffs ($n = 3$). The operator never spontaneously recognized any of these 7 incidents.

Our study involved a single Department with few surgeons, so it is impossible to estimate the influence of experience on exposure risk. While recognizing that laparoscopy is not a high risk intervention and that there may be restrictions on availability of gloves, we nevertheless recommend double gloving in all circumstances where possible.

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Malignant Liver Tumors — Current and Emerging Therapies

P.-A. Clavien (ed)

285 ×220 mm. Pp. 363. Illustrated. 1999. Boston: Blackwell Science. £112. 00

This book is a joy: it is extremely well written by some of the most prominent experts in this field. It is also well illustrated and is really quite comprehensive and well referenced. It is easy to read and, I think, is well balanced. It contains a mixture of chapters on established and emerging therapies, the value of which has yet to be proven. I really enjoyed reading this book. I believe that anyone who is interested in the treatment of liver cancer would find it a very good read and a good source of reference. This is the best book in this area that I am aware of and thoroughly recommend it. The authors have chosen not to cover operative technique but this is readily available elsewhere. Malignant Liver Tumors — Current and Emerging Therapies is a great read.

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Regional Chemotherapy — Theory and Practice

D. A. Kerr and C. S. McArdle (eds)

254 × 175 mm. Pp. 107. Illustrated. 2000. Newark: Harwood Academic. £38.00

Recently, modes of regionally administering chemotherapy and the evaluation of different regimens in a number of malignant tumours have been proposed in order to improve the prognosis of some of these often fatal diseases. This book comprises many aspects of the complex topic of adjuvant and neoadjuvant regional chemotherapy; the comprehensive nature of this work becomes obvious in its structure. The chapters are organized according to the mode of administration and treated tumour entities. The book starts with an introduction to pharmacokinetics of regional chemotherapy. This is followed by a general consideration of intraperitoneal chemotherapy, and different regional chemotherapeutic approaches according to type of tumour (colorectal liver metastasis, malignant melanoma and advanced breast cancer). Before ending with regional chemotherapy of the central nervous system, there is a detailed chapter on cryotherapy. Unfortunately, each chapter is not organized in the same way, which makes the book harder to read than anticipated. Still, the most important aspects for an oncologically-active clinician (including reasoning for the mode of administration, different drugs and phase III trials or, if applicable, randomized controlled clinical trials), are mentioned and discussed. Therefore the volume does contribute to a better interdisciplinary understanding of the complex field of regional chemotherapy. Rather than being an ideal source for all clinicians working in the holistic field of (surgical) oncology, it is an informative supplement for physicians with a main interest in oncology.

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Breast Disease: A Problem-Based Approach

J. M. Dixon and M. Morrow (eds)

233 × 155 mm . Pp. 227. Illustrated. 1999. London: W. B. Saunders. £29.95.

The authors of this book have set themselves a difficult task. Not only do they attempt to tackle breast disease from a problem-based approach, but they aim the textbook at both doctors and ancillary staff involved in day-to-day clinical management. They also aim to cover in 83 pages the whole field of breast pathology, including breast reconstruction, neo-adjuvant therapy and psychological problems after treatment. In some areas the problem-based approach works very well indeed. There are some excellent areas within the book, particularly those relating to the management of early breast cancer and ductal carcinoma in situ. In other areas the problems appear contrived; there is an attempt to force clinical problems into a house style. Additionally, in an attempt to be comprehensive, the significance of the more common breast pathologies is diluted. In several areas the laudable approach to problem-based education is confounded by disparity between text and photographs. For example, in the section on gynaecomastia, the importance of a circumareolar incision is mentioned while the accompanying photograph is of a 16-year-old boy with marked inframammary incision. In the same section the statement is made that the testis should be checked as part of the clinical examination, but no mention is made of why this is important. There are several errors which could have been sorted out at the proof reading stage, for example on page 50 the statement 'this breast mass has a sensitivity of approximately 95%'. The errors include a dangerous recommendation for an adult does of flucloxacillin in the neonate (page 36 – Table 10.1). There are only a few colour plates and the quality of one or two is poor; the first colour plate (Fig. 10.2) for example, shows a green, almost cadaveric, breast. The authors state in their introduction that only the reader can judge if they have succeeded in providing a compact, concise and practical textbook for doctors and ancillary staff involved in the day-to-day management of patients with breast disease. On balance, I feel that this has been a brave attempt. However the result is a series of clinical vignettes that are too variable in quality to recommend this volume for wide readership.

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Scientific Surgery

Mehigan BJ, Monson JRT. Stapling procedure for haemorrhoids versus Milligan-Morgan haemorrhoidectomy: randomised controlled trial. *Lancet* 2000; **355**: 782–5.
Stapled haemorrhoidectomy was less painful with quicker return to normal. Short-term symptom control and functional outcomes were similar in the 40 patients studied.

Bond R, Whyman MR, Wilkins DC, Walker AJ, Ashley S. A randomised trial of different compression dressings following varicose vein surgery. *Phlebology* 1999; **14**: 9–11.
Forty-two patients with bilateral veins were randomized to a different dressing on each leg (TED stockings, Panelast bandages or graduated compression stockings). The dressings were equally tolerated but patients who had Panelast were less mobile.

Raraty MGT, Greaney MG, Blair SD. There is no benefit from 6 weeks' postoperative compression after varicose vein surgery: a prospective randomised trial. *Phlebology* 1999; **14**: 21–5.
The study compared Panelast bandaging for 1 week *versus* bandages for 1 day and TED stockings for 6 weeks. There were no significant differences though most patients discarded their stockings in less than 6 weeks.

Rowsell M, Bello M, Hemingway DM. Circumferential mucosectomy (stapled haemorrhoidectomy) versus conventional haemorrhoidectomy: randomised controlled trial. *Lancet* 2000; **355**: 779–81.
In this study of 22 operations, the stapled procedure reduced Hospital stay and was less painful. Convalescence was reduced without adversely affecting symptom control.

Vaillant JC, Nordlinger B, Deuffic S, Arnaud JP, Pelissier E, Favre JP *et al.* Adjuvant intraperitoneal 5-fluorouracil in high-risk colonic carcinoma: multicenter phase III trial. *Ann Surg* 2000; **231**: 449–56.
Some 133 patients were randomized to receive intraperitoneal plus standard postoperative chemotherapy; 134 had surgery alone. Overall 5-year survival was not different (74 *versus* 69 per cent, respectively), but there appeared to be an advantage in Stage II disease.

Hodgson NC, Malthaner RA, Ostbye T. The search for an ideal method of abdominal fascial closure: a meta-analysis. *Ann Surg* 2000; **231**: 436–42.
In this review of randomized trials, the ideal suture was nonabsorbable and the ideal method was continuous suture.

Voutilainen PE, Haglund CH. Ultrasonically activated shears in thyroidectomies: a randomised clinical trial. *Ann Surg* 2000; **231**: 322–8.
Thirty-six operations were evaluated: use of the new shears reduced operating time by a mean of 35 min without affecting outcome.

Wolmark N, Wieand HS, Hyams DM, Colangelo L, Dimitrov NV, Romond EH *et al.* Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum. *Natl Adjuvant Breast Bowel Project Protocol R-02 J Natl Cancer Inst* 2000; **92**: 388–96.
Some 694 patients with Dukes' B or C tumours were randomized to chemotherapy alone or additional radiotherapy. Radiotherapy did not improve overall 5-year survival but did reduce the rate of locoregional recurrence.

Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P *et al.* Irinotecan combined with fluorouracil compared with fluorouracil alone as first line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000; **355**: 1041–7.
Innotecan improved the median survival from 14.1 to 17.4 months in the 387 patients studied ($P = 0.03$). The authors now consider this first line therapy.

Franks PJ, Moffatt CJ, Ellison DA, Connolly M, Fielden S, Groarke L *et al.* Quality of life in venous ulceration: a randomized trial of two bandage systems. *Phlebology* 1999; **14**: 95–9.
Some 232 patients with a leg ulcer were randomized to one of two four-layer bandage systems (original or Profore): symptoms were compared using quality of life scores. Overall, patients' perceived health improved, particularly if the ulcers healed, but there were no differences between the bandages.

Wedderburn A, Gupta R, Bell N, Royle G. Comparison between low and high-pressure suction drainage following axillary clearance. *Eur J Surg Oncol* 2000; **26**: 142–4.
Some 69 operations were analysed: there were no differences in volume of drainage, rate of complications or duration of Hospital stay.

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Statistics

For detailed guidance on the handling of statistical material consult *Br J Surg* 1991; 78: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

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Set out clearly the objectives of the study, identify the primary and secondary hypotheses, the chosen end-points and justify the sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (*JAMA* 1996; **276**: 637–9).

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Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished and presented in parentheses after the mean values.

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